

NOTEWORTHY SURGICAL CASE STUDIES
FROM ZULEKHA HOSPITAL, DUBAI & SHARJAH
AND ALEXIS MULTISPECIALITY HOSPITAL, NAGPUR.

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FOREWORD



Dear Patrons,

In our second edition of the Zulekha Healthcare Medical Journal, we have once again presented a collection of critical cases that were successfully managed by our experts in Zulekha Hospital UAE and Alexis Multispeciality Hospital, India. The global healthcare crises have magnified with the spread of infections worldwide. As healthcare providers we are putting our best foot forward to cater to our non-covid emergencies as well. The COVID-19 infections have increased the levels of criticality in some cases, challenging our expertise. Nevertheless, our teams have stood up for these. The journal features extracts from some of our experts who have successfully treated complicated newer diseases in gynaecology, cardiology, gastroenterology, paediatric, oncology and general surgery streams. Advances such as image-guided surgeries, fibro-scanning, endoscopic ultrasounds, etc. have evolved medical treatments, ensuring greater patient safety, early detection and diagnosis of diseases. We hope this collection of our experiences and expertise comes in handy to educate and advocate higher quality standards in healthcare, worldwide.

Taher Shams
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NEONATAL DIAPHRAGMATIC HERNIA - A CHALLENGING CASE

A case study by Zulekha Hospital, Dubai



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ABSTRACT

A term female neonate was referred to us postnatally from a neighbouring emirate with a right-sided congenital diaphragmatic hernia (CDH). The baby developed severe pulmonary hypertension and hypoxia which was managed with a combination of high-frequency ventilation, nitric oxide, and inotropic support. The baby was stabilized and was operated on day 4 of life by our paediatric surgeon. There was a further flare-up of pulmonary hypertension in the post-operative period requiring further management. The baby developed severe gastro-oesophageal reflux which is a known complication of CDH.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is always a challenging case for the neonatology team. Despite the vast developments in neonatal care and surgical techniques, CDH cases continue to have a high mortality and morbidity rate^{1,2}. The factors which make it challenging include not only the structural defect but the altered pathophysiology of pulmonary vasculature resulting in severe pulmonary hypertension.

CASE DESCRIPTION

We are presenting a term female infant who was referred to us at 14 hours of age from a neighbouring emirate for the management of right-sided CDH. The baby was born at 41 weeks of gestation with a birth weight of 3.2 kg. The condition was not picked up in antenatal scans. The baby was diagnosed with CDH postnatally when the baby was investigated for significant respiratory distress soon after birth.

On arrival at our unit, the baby was ventilated and was requiring 100% FiO₂. The ventilation mode was changed to high-frequency mode due to poor oxygenation. Ultrasound confirmed the presence of small and large bowel in the right thoracic cavity and the right lung was not visualized. An echocardiogram performed by our consultant paediatric cardiologist showed severe pulmonary arterial hypertension (PAH) with a dilated right ventricle and a moderate-sized patent ductus arteriosus.

Given severe PAH, nitric oxide was administered through the ventilatory circuit to decrease pulmonary artery pressure. Inotropic support was commenced through a central line to increase the systemic pressure above the pulmonary pressure thereby reducing the right to left shunt. After a few stormy days, pulmonary hypertension settled down and the baby was deemed stable for the surgical procedure. She was operated on by our paediatric surgeon on day 4 of admission and the defect in the diaphragm was closed after placing the intestinal contents back in the abdominal cavity.

The postoperative period was stormy as well but settled in a few days with medical management and she was extubated five days after surgery. She required respiratory support for another week.

She remained on parenteral nutrition and establishing feeds was challenging because of significant gastroesophageal reflux (GER). Two weeks post-op she developed a small bowel volvulus requiring emergency laparotomy. 10cm of terminal ileum was resected due to necrotic changes and an end-to-end anastomosis performed. Postoperatively establishing feeds continued to be a big challenge and she was not even tolerating continuous infusion feeds. She was on maximum anti-reflux medical treatment. Also, her suck coordination was not good. Hence it was decided to go ahead with fundoplication and gastrostomy and she was established on full gastrostomy feeds and discharged home. She was followed up closely and established safe oral feeds over months. Her peg was removed at 9 months of age.



DISCUSSION

CDH is an uncommon congenital malformation of the lung with an incidence of 1 in 5000 live births. It is associated with high mortality and morbidity. Despite the improvements in medical and surgical management, the survival rate in CDH babies remains at 60–70%^{1,2}. Our case is a right-sided CDH which is rare (10–15%)^{1,3} compared to left-sided ones (85%).

Antenatal ultrasonography has advanced over the years and well-defined guidelines are in place to aid in the detection of congenital diaphragmatic hernia (CDH). But still approximately half of the neonates born with CDH undergo a prenatal scan that does not diagnose the defect as in our case.

As the herniation occurs during a crucial period of lung development, clinical features of CDH result from the pathologic effects of the herniated viscera on the developing lung. The pathophysiology of CDH is a combination of lung hypoplasia and immaturity associated resulting in persistent pulmonary hypertension of the new-born (PPHN)⁴. Lung hypoplasia occurs on the side of herniation, with the contralateral side being affected to a variable extent. A reduction in total pulmonary vascular bed is noted in CDH along with pulmonary vascular remodelling with medial hyperplasia in small arterioles. There could be associated left ventricular underdevelopment and right ventricular hypertrophy resulting in ventricular dysfunction. Our case had a severe PPHN which responded to pulmonary vasodilator nitric oxide and other supportive treatment modalities^{5,6,7}. In cases with severe refractory PPHN, extracorporeal membrane oxygenation (ECMO) is a useful modality of treatment⁸.

A wide range of factors will help to prognosticate a case of CDH. Among them, the main factors which determine the outcomes are the presence of associated anomalies especially heart disease⁹, degree of lung hypoplasia, and position of the liver. A liver herniation is associated with a worse prognosis. Our case did not have a liver herniation and congenital heart disease was not significant. Prenatal assessment of lung to head ratio (LHR) by ultrasound and comparison to expected LHR at the corresponding gestation is an important tool to assess the severity of pulmonary hypoplasia.

Medical therapy in patients with congenital diaphragmatic hernia is directed toward optimizing oxygenation while avoiding barotrauma. Hence, we were accepting borderline high pCO₂ levels and were trying to keep the ventilatory pressures to the minimum possible to maintain oxygenation^{10,11}. The ideal time to repair a congenital diaphragmatic hernia is unknown. Performing the surgical repair after at least 24 hours post stabilization is considered ideal by many centres, and we follow a similar approach.

CDH survivors face a large number of medical challenges in early infancy and later on in life. Chronic pulmonary hypertension is one of the major complicating factors in CDH but our patient's pulmonary pressures normalized before discharge. A large number of studies have documented the high incidence of GER in infants and children who have CDH. Many respond to medical management but severe cases like ours will need the surgical intervention of fundoplication^{12,13}. Prolonged hospitalization combined with symptoms of GER and delayed initiation of oral feed contributes to the development of oral aversion in infants who have CDH. This was the case in our baby girl and she was discharged home on peg feeding which was reversed at 9 months of age. She is currently thriving well and with a normal neurodevelopmental outcome.

The crux in the management of such complicated neonatal cases is a combined effort from the specialized neonatal nursing and the medical teams and the availability of level 3 infrastructure including nitric oxide. Regular communication and inputs from the

multidisciplinary medical team including neonatologists, paediatric surgeon, paediatric cardiologist, and radiologists enabled us to give a good result for this girl.

REFERENCES

1. Partridge EA, Peranteau WH, Herkert L, et al. Right- versus left-sided congenital diaphragmatic hernia: a comparative outcomes analysis. *J Pediatr Surg* 2016; 51:900.
2. Botden SM, Heiweggen K, van Rooij IA, et al. Bilateral congenital diaphragmatic hernia: prognostic evaluation of a large international cohort. *J Pediatr Surg* 2017; 52:1475.
3. Burgos CM, Frenckner B, Luco M, et al. Right versus left congenital diaphragmatic hernia - What's the difference? *J Pediatr Surg* 2017.
4. Lusk LA, Wai KC, Moon-Grady AJ, et al. Persistence of pulmonary hypertension by echocardiography predicts short-term outcomes in congenital diaphragmatic hernia. *J Pediatr* 2015; 166:251.
5. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). *Pediatrics* 1997; 99:838.
6. Datin-Dorriere V, Walter-Nicolet E, Rousseau V, et al. Experience in the management of eighty-two newborns with congenital diaphragmatic hernia treated with high-frequency oscillatory ventilation and delayed surgery without the use of extracorporeal membrane oxygenation. *J Intensive Care Med* 2008; 23:128.
7. Lawrence KM, Monos S, Adams S, et al. Inhaled Nitric Oxide Is Associated with Improved Oxygenation in a Subpopulation of Infants with Congenital Diaphragmatic Hernia and Pulmonary Hypertension. *J Pediatr* 2020; 219:167.
8. McHoney M, Hammond P. Role of ECMO in congenital diaphragmatic hernia. *Arch Dis Child Fetal Neonatal Ed* 2018; 103:F178.
9. Cohen MS, Rychik J, Bush DM, et al. Influence of congenital heart disease on survival in children with congenital diaphragmatic hernia. *J Pediatr* 2002; 141:25.
10. Canadian Congenital Diaphragmatic Hernia Collaborative, Puligandla PS, Skarsgard ED, et al. Diagnosis and management of congenital diaphragmatic hernia: a clinical practice guideline. *CMAJ* 2018; 190:E103.
11. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. *J Perinatol* 2007; 27:535.
12. Su W, Berry M, Puligandla PS, et al. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. *J Pediatr Surg* 2007; 42:1639.
13. Peetsold MG, Kneepkens CM, Heij HA, et al. Congenital diaphragmatic hernia: long-term risk of gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2010; 51:448.

61-YEAR-OLD MAN RECOVERS FROM SEPTIC SHOCK AND MULTI- ORGAN FAILURE

A case study by Zulekha Hospital, Dubai



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SUMMARY

A 61-year-old man was admitted to Zulekha Hospital, Dubai with a medical history of diabetes mellitus and hypertension. He was a heavy smoker for over 40 years and an alcoholic who was diagnosed with bacterial meningitis complicated by septic shock and multi-organ failure after 129 days of hospital stay. He went home with excellent health conditions.

Sepsis is life-threatening organ dysfunction caused by a deregulated host response to infection. Sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, and killing as many as one in four (and often more). Early identification and appropriate management in the initial hours after sepsis develops, improve outcomes.

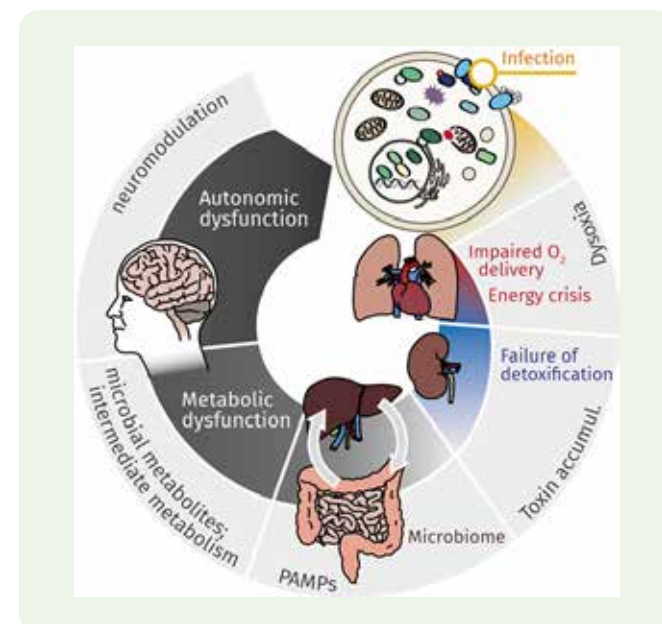
This gentleman was brought by an ambulance with a decreased level of consciousness and hypotension with shortness of breath. He was intubated and started on mechanical ventilation after initial resuscitation. A CT brain done, revealed senile changes. A few hours later investigations revealed that he had a multi-organ failure with severe acidosis and acute kidney injury so renal replacement therapy was started on the same day of admission. Due to the SARS-COV2 pandemic that time, the patient was isolated in a negative pressure room till exclusion of COVID-19 infection.

The cerebrospinal fluid analysis revealed that patient had a bacterial infection which was revealed later in the cultures report as staphylococcus aureus, which also isolated from blood cultures which were covered initially by broad-spectrum antibiotics since admission as empirical treatment.

The patient also developed ARDS and was treated with a lung-protective strategy, he remained under sedation and mechanical ventilation for 16 days then his condition improved and sepsis controlled and kidney function recovered hemodialysis discounted. He successfully had been extubated on day 16 of hospitalization but he developed critical illness polyneuropathy and pressure ulcers in the sacral area, with starting of rehabilitation and physiotherapy he gradually recovered over a period of 4 months till started independently taking his food and walking without assistance. He went home after a long journey of rehabilitation with appreciation to the hospital team.

REFERENCES

1. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock Article in Critical Care Medicine-January 2017, <https://www.researchgate.net/publication/312503654>
2. Sepsis and septic shock: Guideline-based management (CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 87 • NUMBER 1 JANUARY 2020)
3. Acute respiratory distress syndrome in adults Elsevier Point of Care (see details) Updated November 4, 2019.
4. ARDS Definition Task Force et al: Acute respiratory distress syndrome: the Berlin Definition. JAMA. 307(23):2526-33, 2012



A CASE OF PARAPLEGIA

A case study by Zulekha Hospital, Dubai



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SUMMARY

A 62-year-old Philippine gentleman, presented with a one-year history of progressive leg weakness and inability to walk. He had lost his ability to stand and walk. He was paralyzed with urinary incontinence.

His neurological examination showed a sensory level at the T5 level, a force of 1-2/5 in both lower extremities, 4+ hyperreflexia and bilateral clonus.

His spinal MRI revealed a large 2.5 cm x 1.3 cm Intra-dural extra-metallary spinal tumour at T5-T6 level, compressing the spinal cord significantly (Fig 1).

After discussing the risks and benefits of surgery and the outcome, considering long term course of functional paraplegia, he decided to remove this tumour.

Under general anaesthesia, a prone position, after prep and drape, a laminectomy of T4 and T5 was performed and after opening the dura, tumour which was well-defined and capsulated, was detached from the spinal cord and was removed gross-totally and en-block (Fig 2).

POST-OPERATIVE COURSE:

The day after the surgery, the patient started moving his legs and on day 5 post-surgery, he was able to stand on his legs and take 1-2 steps. With this fast improvement, we expect him to improve significantly over the course of 2-3 months of physiotherapy. His urinary function has also improved significantly.

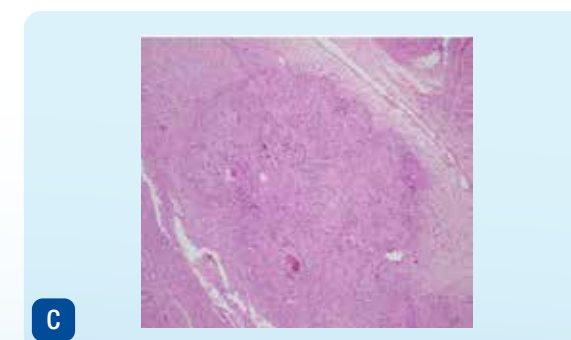
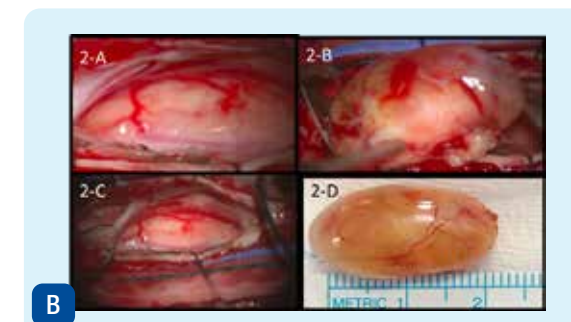
The pathology result was consistent with Schwannoma, which is a benign tumour and does not require any further treatment (Fig. 3).

DISCUSSION:

Spinal cord tumours, based on the involved compartment, are divided as 1-Extradural (55%), like metastasis or primary vertebral tumours, or 2-Intradural Extradural (40%), like meningioma or nerve sheath tumours (Schwannoma, Neurofibroma), and finally, 3-Intramedullary tumours (5%), which arises from the spinal cord itself, like Ependymoma and Astrocytoma. This patient's tumour was from the second category. These tumours are benign and slow-growing tumours. Early diagnosis and management are associated with a very good outcome. Although the most important prognostic factor is preoperative neurological status, however, this case showed that we should not be disappointed with the result and we should take the tumour out and give a chance to the spinal cord for recovery.

Fig

- A** - MRI of Dorsal spine after injection of Gadolinium, showing a spinal tumour at the T4-T5 level and compressing the spinal cord.
- B** - Different stages of tumour resection. 2-A shows the Intradural Extradural tumour; 2-B shows en block resection of the tumour; 2-C shows the cavity and impression of the tumour over the spinal cord and 2-D shows the size and shape of the tumour.
- C** - Pathologic feature of the tumour (Schwannoma) which did not show any evidence of malignancy.



62 YEAR OLD MAN RECOVERS FROM SUBARACHNOID HAEMORRHAGE

A case study by Zulekha Hospital, Dubai



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CASE REPORT:

A 62-year-old local UAE resident presented with sudden onset of headaches. Although he was seen in many hospitals, no Computed Tomography Scan (CTS) was done. Finally, two weeks later, he was seen by a neurologist and subarachnoid haemorrhage was suspected. He was referred to us immediately for final diagnosis and treatment.

We admitted the patient and performed a cerebral Digital Subtraction Angiography (DSA), which confirmed a 7 mm x 4 mm anterior communicating artery aneurysm (ACoM). (Fig. 1-A and 1-B)

We discussed the risks and benefits of two ways of treatment including open craniotomy and microvascular clipping versus endovascular coiling of his brain aneurysm. He selected the second option and underwent the novel technique of endovascular coil occlusion of his brain aneurysm without performing a craniotomy. Eight coils were deployed inside his aneurysm and the aneurysm was completely occluded. (Fig. 1-C)

Postoperatively, the patient remained neurologically intact and was discharged home on day 3 after coiling. He came back to the clinic one week later without any symptoms.

DISCUSSION:

Brain aneurysms are a weak point on the blood vessel's wall and subsequent outpouching and ballooning out under hemodynamic stresses. The wall of these aneurysms are very thin and therefore, prone to rupture. Hypertension and smoking are well-known causes that have been proved to be associated with the development and the growth of the brain aneurysms. However, some brain aneurysms are also run in the family, which highlights the effect of genetic factors in the creation of the brain aneurysms. As we know, some collagen vascular disease and polycystic kidney diseases are associated with a brain aneurysm.

Brain aneurysms, if untreated, have a 1-2% annual risk for rupture and bleeding. Bleeding from a ruptured aneurysm, which is called a subarachnoid haemorrhage, has a very bad outcome and morbidity and mortality are more than 50%. Rebleeding, vasospasm, brain swelling, electrolyte imbalance and hydrocephalus are some of the main complications of aneurysmal subarachnoid haemorrhage.

Therefore, by early detection and securing the aneurysm we can prevent rebleeding and lots of other complications. Performing a plain CT Scan is mandatory in every patient with the history of sudden onset of the worst headaches in his or her life.

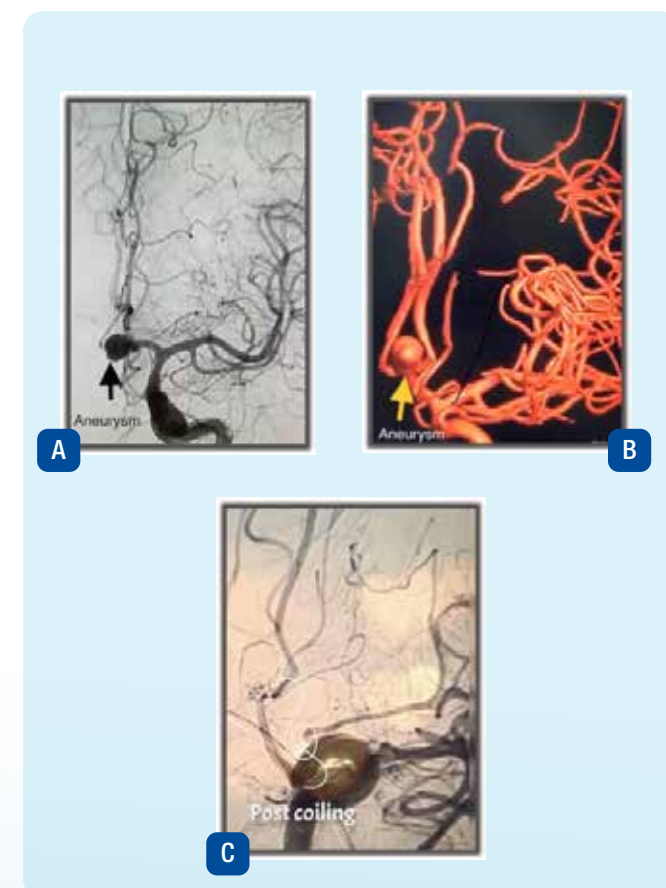
If clinically suspected but, CT scan is negative, we can perform a lumbar puncture or a CT angiography and if positive or still suspected, a cerebral DSA will confirm the diagnosis.

If angioarchitecture of an aneurysm favours endovascular coiling,

especially having a small neck in relation to the size of its dome, we will proceed with coiling. Otherwise, if coiling is technically not possible or unsafe, then microsurgical clipping will be performed to secure the aneurysm as soon as possible.

Fig.

- A** - Cerebral digital subtraction angiography, showing an anterior communicating artery aneurysm.
- B** - 3-Dimensional reconstruction of cerebral angiography to see more details about the shape of the aneurysm.
- C** - Post coiling angiography, showing complete occlusion of the aneurysm.



A RARE CASE OF ACUTE LIMB-GIRDLE WEAKNESS IN A YOUNG FEMALE - A COMPLETELY REVERSIBLE AUTOIMMUNE PHENOMENON FOLLOWING TREATMENT OF THE UNDERLYING CAUSE.

A case study by Zulekha Hospital, Dubai



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BACKGROUND:

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular junction characterized by the production of autoantibodies directing against the molecules of neuromuscular transmission.³ It's well known that 10-15% of MG patients have thymoma.¹ The association of MG with extrathymic malignancies are rare but has been reported with lymphoma and lung cancer simultaneously with the MG. Here we present a case of Acetylcholine receptor antibody-positive MG with asymmetrical limb-girdle weakness unlike the usual paraneoplastic form (neck and bulbar weakness) and has antedated the breast cancer by 6 months. She became free of immunomodulatory drugs once the Acetylcholine receptor antibodies became negative after successful treatment of myasthenia gravis and malignancy.

Keywords: Myasthenia Gravis, Carcinoma Breast, Paraneoplastic Neurological Syndrome

1.1 CASE REPORT

A 35-year-old lady was seen in Neurology clinic with tiredness, fatigue, unable to carry her baby, difficulty in climbing stairs, and getting up from the sitting position of two days duration. She told it was of acute onset and asymmetrical (left more than right) and she didn't report any other symptoms like pain, double vision, drooping of eyelids or difficulty in swallowing. There was no history of fever, joint pains, oral ulcers or weight loss. She had a normal appetite. She was already evaluated by a neurologist in another facility by MRI brain and cervical spine and told her the possibility of demyelinating disorder in view of acute and more of left-sided weakness and was suggested lumbar puncture. On examination, she had minimal bilateral fatigable ptosis (right>left). Eye movements were full range. The power of neck flexors and extensors were 5/5 by MRC grading. Upper limbs and lower limbs were 5/5 involving all proximal and distal groups. However, the arm abduction and leg raising time were 30 seconds. Single breath count was 25. The deep tendon reflexes were normal and the plantar was extensor. There was no history of any fever or diarrhoea preceding this event. She was not on any medications including levothyroxine or statins. She was investigated by complete blood count, vitamin D levels, serum electrolytes, CPK and TSH which were all within normal limits. The ice pack test and Neostigmine test were positive. We used the standard low-frequency repetitive nerve stimulation (RNS) test which is one of the most sensitive diagnostic tests in patients with Neuromuscular Junction disorders to evaluate patients muscle weakness. We first performed nerve conduction study (NCS) in upper and lower limbs which were normal in distal latency, velocity and amplitude. Then 3 HZ (slow)

RNS performed in two warm (33-35 degree Celsius) trapezius muscles that were immobilized as best as possible for 10 impulses; then it was repeated three times 1 minute apart. More than 10% decrement was seen in the amplitude and the area of the first to fourth CMAP. The needle EMG was normal and the decrement became remarkable after 3-4 minutes of post-exercise for 1 minute. These findings were suggestive of postsynaptic NMJ disorder. The findings were presented in Figures 1 and 2. Her acetylcholine receptor antibody levels were elevated (Figure 3) and anti-musk antibody was negative. Antinuclear antibodies were negative. Serum angiotensin-converting enzyme levels were normal. The CT thorax didn't reveal any thymic enlargement. She was admitted for treatment and was started on Intravenous immunoglobulin 400 mcg/kg/day for 5 days and discharged with oral steroids in gradually escalating doses along with pyridostigmine. Once her improvement became steady, the steroids were gradually tapered and stopped. She was initiated on steroid-sparing agent mycophenolate mofetil. Six months later she had presented to general surgeon with pain and swelling in the left breast and was diagnosed to have carcinoma of the left breast. She underwent a modified radical mastectomy followed by adjuvant chemotherapy. We followed her periodically as the association with breast cancer in the literature is not found and wasn't sure if she has autoimmune MG/ paraneoplastic MG associated with breast cancer. Once her acetylcholine receptor antibody became negative (Fig 3) we planned to stop her immunomodulatory therapy mycophenolate mofetil. She was followed up regularly for one year after stopping the mycophenolate mofetil and there was no recurrence of any neurological symptoms.

Figure 1. Nerve conduction studies

Figure 2. RNS test findings

Figure 3. Acetylcholine receptor antibody levels (serial studies)

1. 25/3/2019; Acetyl choline receptor antibodies; 1.48; Reference (Negative <0.25; positive >0.40)
2. 25/9/2019; Acetyl choline receptor antibodies; 0.32; Reference (Negative<0.25; positive>0.40; 0.25-0.40 Equivocal)
3. 13/1/2020; Acetyl choline receptor antibodies; 0.03; Reference (Negative <0.25; Positive ;> 0.40)

DISCUSSION

Although the association between MG and thymoma is widely recognized, the relationship between MG and other neoplasms remain unclear.¹ MG has been rarely reported in patients with B cell lymphoma and even more rarely as presenting symptoms.⁴ Our patient has very interesting facts when compared to other extrathymic neoplasms 1) Usually paraneoplastic MG presents with bulbar and neck muscle weakness whereas our patient has presented with limb-girdle weakness and that too predominantly asymmetrical which has made other physicians think about the demyelinating event. 2) The MG has antedated the malignancy by 6 months 3) Resolution of acetylcholine receptor antibody to undetectable levels after the surgical and adjuvant chemotherapy of breast cancer. The increased tendency to present cancer found in many autoimmune diseases is due to immune dysregulation that elicits both the autoimmune cascade and limits the defensive response to cancer cells.⁴ Of the different extrathymic malignancies in MG patients, we can categorize haematological malignancies as especially frequent. In our patient, it's difficult to say the cancer development is due to immunosuppression as she has used it only for one year after which we have stopped as there was a progressive decrease in the acetylcholine receptor antibody levels to undetectable levels. The acetylcholine receptor antibody presents an uncertain association with tumours such as its positivity doesn't help characterize the condition as a paraneoplastic syndrome.⁵ Our patient has improved both clinically and showed negative titers of antibodies after surgical resection and chemotherapy which is a possible predictor of oncological response. To our knowledge, this is the first case of possible causality between breast cancer and myasthenia gravis as a paraneoplastic syndrome presenting a few months before the onset of malignancy. In conclusion, this case was atypical MG which has antedated the malignancy by a few months and could be early paraneoplastic manifestation which can confuse a clinician by acute asymmetrical weakness. Hence it's essential to remember paraneoplastic manifestation whenever the manifestations of a neurological syndrome don't fit with the normal phenotypical presentation of autoimmune MG in which case serial follow up of patients for malignancy is very essential.

REFERENCES

1. Evoli A, Batocchi AP, Tonali P, Marciano M. Risk of cancer in patients with myasthenia gravis . Ann N Y Acad Sci. 1998;841:742-5

2. Monden Y, Uyama T, kimura S, Taniki T.Extrathymic malignancy in patients with myasthenis gravis. Eur J Cancer .1991 ;27(6); 745-7

3. Spillane J , Beeson DJ,Kullmann DM. Myasethenia and related disorders of the neuromuscular junction. J Neurol Neurosurg Psychiatry 2010;81;850-7

4. Levin N, Abramsky O, Lossos A,Karussis D,Siegal T, Argov Z et al. Extrathymic malignancies in patients with myasthenia gravis. J Neurol Sci.2005;237(1-2):39-43

5. Dalmau J, Rosenfeld M Update on paraneoplastic neurological disorder. Commun oncol 2010;795);219-224.

Figure 1. Nerve conduction studies

Motor Nerve Conduction:						
Nerve and Site	Latency	Amplitude	Segment	Latency Difference	Distance	Conduction Velocity
Peroneal R						
Anticub	4.2 ms	4.8 mV	Extensor digitorum brevis	4.2 ms	60 mm	60 m/s
Posterior Tibial	11.0 ms	3.8 mV	Anticub (Study 2nd)	6.8 ms	230 mm	60 m/s
Tibial R						
Anticub	3.7 ms	21.1 mV	Abductor hallucis-Anticub	3.7 ms	60 mm	100 m/s
Posterior Tibial	17.3 ms	18.2 mV	Anticub-Posterior Tibial	13.6 ms	140 mm	50 m/s
Peroneal L						
Anticub	4.0 ms	5.4 mV	Extensor digitorum brevis	4.0 ms	60 mm	60 m/s
Posterior Tibial	11.1 ms	8.1 mV	Anticub (Study 2nd)	7.1 ms	230 mm	60 m/s
Tibial L						
Anticub	3.4 ms	21.4 mV	Abductor hallucis-Anticub	3.4 ms	60 mm	100 m/s
Posterior Tibial	13.4 ms	13.2 mV	Anticub-Posterior Tibial	10.0 ms	140 mm	40 m/s
Median R						
Wrist	3.6 ms	17.3 mV	Abductor pollicis brevis	3.6 ms	60 mm	60 m/s
Elbow	7.8 ms	17.3 mV	Wrist-Elbow	4.2 ms	230 mm	60 m/s
Ulnar R						
Wrist	2.8 ms	10.8 mV	Abductor digiti minimi	2.8 ms	60 mm	60 m/s
Elbow	5.2 ms	9.8 mV	Wrist-Elbow	2.4 ms	230 mm	60 m/s
Median L						
Wrist	3.3 ms	13.7 mV	Abductor pollicis brevis	3.3 ms	60 mm	60 m/s
Elbow	7.5 ms	13.0 mV	Wrist-Elbow	4.2 ms	230 mm	60 m/s
Ulnar L						
Wrist	2.9 ms	12.0 mV	Abductor digiti minimi	2.9 ms	60 mm	60 m/s
Elbow	5.0 ms	11.6 mV	Wrist-Elbow	2.1 ms	230 mm	60 m/s

Figure 2. RNS test findings

F Wave Studies		
Nerve	NI Latency	F Latency
Peroneal R	11.0	42.1
Tibial R	11.3	44.5
Peroneal L	11.1	42.1
Tibial L	11.4	43.8
Median R	7.8	38.7
Ulnar R	7.2	37.1
Median L	7.9	38.1
Ulnar L	8.0	38.1

Sensory Nerve Conduction:						
Nerve and Site	Count	Peak Latency	Amplitude	Segment	Latency Difference	Distance
Tibial R						
Lower leg	1.0 ms	2.7 ms	26 µV	Anticub-Lower leg	2.0 ms	120 mm
Tibial L						
Lower leg	1.0 ms	2.4 ms	19 µV	Anticub-Lower leg	1.8 ms	110 mm
Median R						
Wrist	2.0 ms	3.8 ms	45 µV	Digit II (Index Finger)-Wrist	2.0 ms	110 mm
Ulnar R						
Wrist	2.1 ms	2.9 ms	33 µV	Digit V (Little Finger)-Wrist	2.0 ms	110 mm
Median L						
Wrist	2.0 ms	2.8 ms	41 µV	Digit II (Index Finger)-Wrist	2.0 ms	110 mm
Ulnar L						
Wrist	2.2 ms	2.9 ms	41 µV	Digit V (Little Finger)-Wrist	2.2 ms	110 mm

Figure 3. Acetylcholine receptor antibody levels (serial studies)

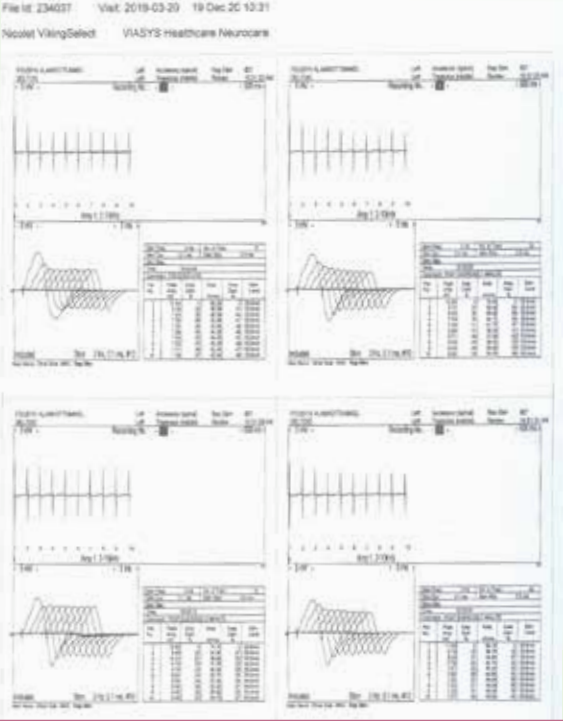


IMAGE GUIDED SURGERY

A randomized controlled study by Zulekha Hospital, Sharjah



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BACKGROUND:

Recent success with ICG guided laparoscopic cholecystectomy has led to its adoption by many. However, whether it makes the operation safer by reducing the possibility of CBD injury, is yet to be evaluated scientifically

Aim: To compare the rate of CBD injury in groups with and without the use of ICG, during laparoscopic cholecystectomy

Methods: Over 2 years from the beginning of January 2017, all patients undergoing laparoscopic cholecystectomy were randomized to ICG and no ICG groups. ICG group patients received 2ml of 2.5mg/ml ICG, intravenously an hour before surgery. Laparoscopic cholecystectomy was then performed using near-infrared (NIR) scope for both groups. In ICG group switching to NIR mode showed fluorescence of extra-hepatic biliary tract. The operative time and rate of CBD injury of both groups were compared.

Results: 102 patients in each group were comparable in terms of age, the ratio of male patients, body mass index, ASA grades and rate of complicated cholecystitis (acute/acute or chronic

cholecystitis, biliary pancreatitis, choledocholithiasis without signs of CBD stones at the surgery or after endoscopic retrograde cholangiopancreatography (ERCP). The median operative time was 50 minutes in the ICG group and 53 minutes in the no-ICG group, with no significant difference between the two. There were no CBD injuries in either group.

CONCLUSIONS:

ICG acts as a roadmap and provides early identification of extra-hepatic biliary anatomy and has the potential to add safety; though future studies with bigger sample size can reliably verify the hypothesis by comparing the actual CBD injury in each group.

Conclusion on safety: Safe dissection is a basic surgical skill and cannot be replaced, but can be enhanced by technology (ICG fluorescence). Avoiding over-reliance on technology is an important warning as there is a finite risk of pseudo-safety with increased risk of injury.

CHARACTERISTICS	NO ICG GROUP	ICG GROUP
NUMBER OF PATIENTS	102	102
AGE, YEARS, MEDIAN	42 (12-62)	48 (20-67)
MALES (PERCENTAGE%)	33	35
BODY MASS INDEX, KG/M2, MEDIAN	28 (23- 35)	30 (22- 37)
ASA SCORE (PERCENTAGE%) 1-2	78	75
ASA SCORE MORE THAN OR EQUAL TO 3 (%)	22	25
RATE OF COMPLICATED CHOLECYSTITIS (PERCENTAGE %)	32	37
OPERATIVE TIME (MEDIAN, RANGE) MINUTES	53 (30- 137)	50 (25- 124)
CBD INJURY	NONE	NONE

All unselected patients
needing laparoscopic
cholecystectomy from
Jan 2017-19

Randomize

102
With ICG

102
Without
ICG

Compare rate of CBD
injury and operative time



Pics with ICG fluorescence to identify biliary anatomy

	NUMBERS	PERCENTAGE (%)
Total patients in ICG group	102	
Anatomy Identifiable prior to ICG (in normal light mode)	22	22
Anatomy Identifiable before dissection (in NIR (near infrared) mode)	62	61
Anatomy Identifiable after dissection (in NIR (near infrared) mode)	25	25
Total number with anatomy identifiable in NIR mode	87	85
Anatomy not identifiable (in NIR (near infrared) mode)	15	15
Pseudo-safety/ increased risk (dissecting close to bile duct, endangering safety of its vascularity)	2	2

Rate of visualization OR non-identifiability of anatomy in ICG group indicative of safety addition by use of ICG fluorescence

Evaluation of safety: As CBD injury rate is as low as 0.5%, very large sample size is needed to evaluate actual safety. Visualization and identification of correct anatomy is an indirect indicator of safety of procedure, by helping surgeon to reduce potential CBD injury.

Increased safety by use of ICG	No additional safety or Increased risk* by use of ICG
In 85% cases, anatomy identifiable by ICG fluorescence: acts as roadmap of biliary anatomy to increase safety by avoiding dissection close to bile duct and ascertaining the correct place of safe dissection	In 22% patients, anatomy is identifiable in normal light without ICG, hence no additional safety expected by ICG use
Confirmation of anatomy: switching to NIR mode as many times as desirable throughout procedure, to confirm the correct, safe dissection, away from vital structures	In 15% patients, fluorescence was not obtained by ICG, (impacted stone, severe acute on chronic cholecystitis and empyema) Conventional dissection in normal light needed in such cases to reveal the critical view of safety.
	*Pseudo-safety/increased risk: Upon establishing the location of common bile duct by ICG, possibility of dissecting close to bile duct, endangering safety of its vascularity; happens in early learning curve though finite possibility of such event was 2%

MANAGEMENT OF NON-HODGKIN'S LYMPHOMA CASE WITH LARGE MEDIASTINAL MASS

A case study by Zulekha Hospital, Sharjah



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PhD (Medical Oncology), MS (Internal Medicine), MBBCh (Surgery, Medicine and ESMO (European Society Member of Oncology)

ABSTRACT

Lymphomas are neoplasms of lymphocytes and their precursor cells [1]. Malignant lymphomas can be broadly divided into Hodgkin's disease and Non-Hodgkin's Lymphoma – NHL [2]. The incidence of NHL is rising worldwide and is the 5th most common malignancy in United States [3]. In UK, NHL accounts for 2.4% of all cancers registered in England and Wales and 2.6% of all cancer deaths. NHL may arise in lymph nodes as well as at a wide variety of extra-nodal sites. The most common lymphomas are of diffuse large B-cell type -DLBCL (33%) followed by B-cell follicular lymphomas. Primary Mediastinal B-cell Lymphoma (PMBL) is a subtype of diffuse large B cell NHL. DLBCL are considered intermediate grade NHL [4].

Rituximab (Rituxan) has changed the treatment paradigms and outcomes for all CD20+ NHL and represents arguably the most noteworthy advance in lymphoma treatment over the past decade. In patients with NHL, the addition of rituximab to standard treatment significantly enhanced response to therapy and overall outcomes [5].

THE PATIENT AND CLINICAL PRESENTATION

A 30 years old lady with a diagnosis of a stage 11 B primary mediastinal diffuse B-cell lymphoma (a type of NHL) presented with two months history of intermittent fever, night sweats, breathlessness, hoarse voice and a short history of a swollen right arm and a puffy face and neck. On admission she was diagnosed with Superior vena cava syndrome.

DIAGNOSTIC WORKUP

A number of investigations were carried out to diagnose, stage and grade the disease as well as to decide on an appropriate and effective treatment plan. Investigations were also performed to determine the response to initial treatment. These investigations are discussed below.

HISTORY AND PHYSICAL EXAMINATION (PE)

There was a history of B symptoms such as fever, night sweats and weight loss. A detailed physical examination of all lymph nodes was performed. Abdominal examination was unremarkable. There was a previous history of DVT (Deep vein thrombosis) of right internal jugular and right subclavian vein and therefore the patient was on Warfarin. The patient had a hoarse voice as a result of pressure on the right recurrent laryngeal nerve.

LABORATORY STUDIES

Full blood count including erythrocyte sedimentation rate, serum lactate dehydrogenase and Beta -2 microglobulin measurement and serum electrolytes, urea and creatinine assessment was done.

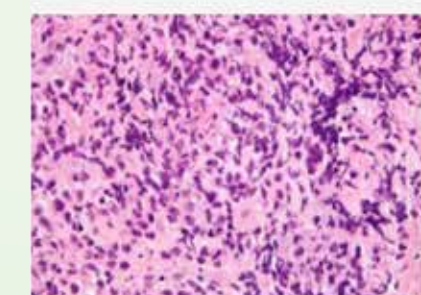
RADIOGRAPHIC IMAGING

A CT scan of neck, thorax, abdomen, and pelvis demonstrated a 10.1 * 7.2 cm mass in the superior mediastinum. A peritracheal lymph node and a further mediastinal lymph node at the superior level of aortic arch were noted [6].



BIOPSY OF THE PRIMARY SITE

Along through CT-guided biopsy of the primary lesion (mediastinal mass) was carried out to obtain histological diagnosis. Pathology report confirmed a diffuse large B-cell lymphoma. A definitive diagnosis is made only by biopsy of pathologic lymph node or tumour tissue [6]. Guidelines from NCCN also recommend biopsy for the accurate diagnosis of Diffuse large B cell lymphomas. Nice further emphasis on use of excisional biopsy in most cases as it is a straight forward way to obtain correct diagnosis. In other cases, core needle biopsy can be carried out [7].



CELL SURFACE MARKERS

The tumour was found to be CD20 positive which verifies its B-cell nature. PMBL is a B-Cell tumour and its B-cell phenotype can also be determined by CD20 positivity^[6].

Dunleavy and Wilson listed Detailed history and Physical examination, evaluation of haematological and biochemical parameters, CT of chest, abdomen, pelvis and bone marrow Aspirate biopsy as part of diagnostic workup for Primary Mediastinal B-cell Lymphoma^[8].

POSITRON EMISSION TOMOGRAPHY (PET-CT)

British society for Haematology recommends carrying out base line PET-CT scan in all patients at the time of diagnosis and bone marrow biopsy is not required if PET-CT scan is already performed^[35].

The study by Khan and colleagues concluded that PET-CT was highly accurate for diagnosing Bone marrow involvement in DLBCL with sensitivity and specificity of 94% and 100% compared to 40 and 100% for marrow biopsy^[10]. Imaging working group recommends optimal use of PET-CT in staging and response assessment of lymphomas^[11].

MANAGEMENT OF PMBL

Management of the stage 11 B PMBL was based on the prognostic factors (age etc), stage (extent of disease) and histological subtype, which is an indication of aggressiveness and dissemination. Treatment modalities included chemotherapy, immunotherapy and External beam Radiotherapy (EBRT).

CHEMOTHERAPY

Patient received 6 cycles of Rituximab-CHOP-21 along GCSF support as first line treatment for management of intermediate grade DLBCL. With close monitoring of patient general status and proper management of any chemotherapy immediate or delayed side effects.

R-CHOP-21.

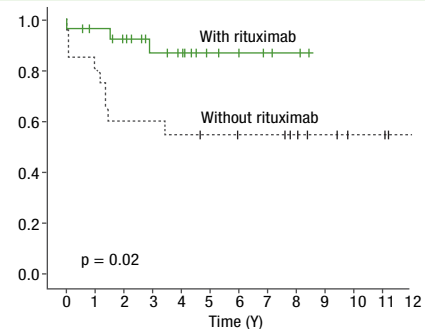
NHL tends to be less localized than Hodgkin's disease hence Chemotherapy has gained a more predominant role in its management over the past decade^[12]. In patients with PMBL initial treatment is with anthracycline containing regimen such as CHOP^[5]. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is a standard chemotherapy regimen for the treatment of DLBCL in low and intermediate prognostic groups^[12].

IMMUNOTHERAPY

Patient received immunotherapy in the form of Rituximab. Rituximab is a monoclonal antibody against the CD20 B-cell antigen. Treatment was administered at 21 days.

A study reported a significant benefit of the combined immuno-chemotherapy in both patients with low risk IPI and those with high risk IPI. Overall response rate was 94% with a complete response rate of 61%. The long-term results of the study are quoted by Fuggier^[13].

This figure shows superiority of R-CHOP over conventional CHOP and makes it the new standard for patients with aggressive NHL^[14]



GROWTH FACTORS

G-CSF (granulocyte colony-stimulating factor) was prescribed to be given from days 4-12 to deal with neutropenia. GCSF is a myeloid growth factor for the production of functionally active neutrophils and is approved for clinical use to reduce the incidence of febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy. The most common side effect observed with the use of G-CSF is mild to moderate bone pain^[15].

Patient response evaluation after 4th chemotherapy session, by PET-CT showed : regressive course of previously described mediastinal mass lesion without residual FDG uptake within, picture consistent with excellent metabolic response.

CONSOLIDATION RADIOTHERAPY

On completion of chemotherapy, patient had a CT and PET scan which showed complete metabolic response to R-CHOP treatment, Patient received consolidation radiotherapy to the mediastinum and right neck.

DISCUSSION

British society for Haematology recommends carrying out base line PET-CT scan in all patients at the time of diagnosis and bone marrow biopsy is not required if PET-CT scan is already performed . BM biopsy is indicated if it can change risk management e.g. if a patient presents with extra-nodal disease there is a risk of CNS involvement and BM can confirm lymphomatous infiltration leading to CNS prophylaxis. These guidelines further recommend carrying out core or excisional biopsy to obtain histological diagnosis. Interim PET is often employed in clinical practice to assess the efficacy of treatment and to eliminates the presence of disease progression. Various studies have indicated that interim PET is a powerful prognostic indicator in HL and aggressive NHL^[10]. Thus, interim PET can be used to customize treatment but there is no definitive conclusion that it will affect the outcome^[38, 39]. Hence the working group recommended use of interim PET to assess early response because it is better than CT alone and only alter treatment based on interim PET-CT findings if there is strong evidence of progression^[11].

The study by Khan and colleagues concluded that PET-CT was highly accurate for diagnosing Bone marrow involvement in DLBCL with sensitivity and specificity of 94% and 100% compared to 40 and 100% for marrow biopsy^[10]. PET diagnosed all clinically relevant marrow involvement and biopsy did not upstage any patient. PET positive marrow involvement is unlikely to show clinically significant marrow involvement identified by biopsy. Similarly, cases with limited focal deposits far from iliac crest are unlikely to gain from biopsy^[10].

Conventional methods of lymphoma treatment, including chemotherapy and radiation, are associated with toxicity and lack specific antitumor-targeted activity. Cell-surface proteins, such as CD19, CD20, and CD22, are highly expressed on B-cell lymphomas and represent key potential targets for treatment.

Antibody therapy directed against CD20 has had the most important clinical impact to date. CD20 is thought to be involved in the regulation of intracellular calcium, cell cycle, and apoptosis. CD20 is not shed, modulated, or internalized significantly upon antibody binding, thus making it an ideal target for passive immunotherapy.^[15]

Rituximab represents a paradigm shift in treatment of B-cell NHL; it marks the beginning of a new age of targeted therapies in oncology, Benefits have been sustained among all age groups, and the drug has been safe and well tolerated in elderly patients as well.

Addition of Rituximab to CHOP followed by mediastinal RT resulted in 5-year PFS of 75-85%. Overall survival of patients with NHL has also improved over the last two decades. While some of this improvement may stem from earlier or more precise diagnosis and better supportive care^[14].

CONCLUSION

Treatment of PMBL has evolved over the years. Combined modality treatment in the form of anthracycline-containing chemotherapy followed by mediastinal irradiation is treatment of choice for stage11a PMBL. Addition of Rituximab improves response rate and overall survival. GCSF support reduces myelotoxicity and treatment time. PET-CT can also be used instead of Bone marrow aspirate to correctly indicate bone marrow involvement. It is recommended to use Baseline PET-CT scan and interim and end of combined modality treatment PET-CT scan. Professional implications include appropriate use of antiemetics, monitoring of blood counts as well as cardiac function and patient education to prepare him/her for self-care.

REFERENCES

1. Magrath I. Introduction: Concepts and controversies in Lymphoid neoplasia. In: Magrath I, editor. The Non-Hodgkin's Lymphomas. 1997.
2. Bomford C, Kunkler I. Walter and Miller' Textbook of Radiotherapy: radiation physics, therapy and oncology. 3rd ed. Edinburgh: Churchill Livingstone; 2003.
3. Tsang R, Gospodarowicz M, & Sullivan B. Staging and management of localized non-Hodgkin's lymphomas: variations among experts in radiation oncology. Int. J. Radiation Oncology Biol. Phys. 2002;52(3):643-651.
4. Evans L, Hancock B. Non-Hodgkin Lymphoma. The Lancet, 2003;362:139-146.
5. Souhami R and Tobias J. Cancer and its management. Oxford, Blackwell Science Ltd; 2003.
6. Besien K, Kelta M, Bahaguna P. Primary Mediastinal B-Cell Lymphoma: A review of Pathology and Management. Journal of Clinical Oncology. 2001;19(6):1855-1864.
7. National guideline Alliance. Non-Hodgkin's Lymphoma diagnosis and management. NICE guideline [NG52]: methods, evidence and recommendations. National Institute for Health and Care Excellence. 2016.
8. Dunleavy K, Wilson W. Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: do they require a unique therapeutic approach? Blood. 2015;125(1):33-39.
9. Molina A, Non-Hodgkin's lymphoma. In: Pazdur R, Coia L, Hoskins W. et al. Editors. Cancer Management: A Multidisciplinary Approach. Medical, Surgical, & Radiation Oncology. New York: PRR Inc; 2001.
10. Barrington S, Mikhaeel N, Kostakoglu L, Meignan M, Hutchings M, Mueller S, et al. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. Journal of Clinical Oncology. 2014;32(27):3048-3058.
11. Cheson B. Role of functional imaging in the management of lymphoma. J Clin Oncol. 2011;29(14):1844 - 1854.
12. Aisenberg A, Chen Y. The Lymphomas' In: Wang C. editors. Clinical Radiation Oncology Indications, Techniques, and Results. New York: Wiley-Liss; 2000.
13. Vose J, Link B, Grossbard M, et al. Phase 11 study of Rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. Journal of Clinical Oncology. 2001;19(2):389-397.
14. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. Annals of Oncology. 2003;14(4):520-535.
15. Hutchings M, Barrington S. PET/CT for therapy response assessment in lymphoma. J Nucl Med. 2009;50:21S-30S, 2009 (suppl 1)

ROLE OF OMEGA-3 POLYUNSATURATED FATTY ACIDS IN TREATMENT OF NASAL POLYPOSIS

A single-blinded randomised controlled trial by Zulekha Hospital, Sharjah



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ABSTRACT

Background: Nasal polyposis is a common disease with steroids either systemic or topical being the key element in its medical treatment. With known side effects of systemic steroids, other anti-inflammatory agents should be evaluated, preferably the natural ones.

Objective: To evaluate the role of omega-3 polyunsaturated fatty acids in the treatment of nasal polyposis.

Methods: This is a single-blinded randomized-controlled trial including 164 patients with grade II nasal polyposis receiving a short course of systemic steroids until subsidence of polyposis. Patients were distributed equally after into 2 groups according to maintenance therapy with group I receiving omega-3 fatty acids in a dose of 3 g per day with local budesonide nasal spray and group II receiving only local budesonide nasal spray. Both groups were compared regarding incidence and grade of recurrence of polyposis and duration from onset of maintenance therapy to onset of recurrence.

Results: A nonsignificant effect for omega-3 was found on the incidence of recurrence of nasal polyposis ($P=0.1$) and the grade of recurrent polyposis ($P=0.66$). However, omega-3 intake had a highly significant effect on delaying the incidence of recurrence of polyposis ($P<0.0001$).

Conclusion: Omega-3 fatty acid has a beneficial effect on delaying the incidence of recurrence of nasal polyposis through its proven anti-inflammatory mechanism of action. This minimizes the need for systemic steroid administration with its known side effects. Omega-3 fatty acids supplementation should be considered while tailoring the maintenance regimen for medical treatment of chronic rhinosinusitis with nasal polyposis.

Keywords: omega-3 fatty acids, polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, nasal polyps, anti-inflammatory agents, steroids, sinusitis, recurrence

INTRODUCTION

Nasal polyposis is a common disease of nose and paranasal sinuses, affecting up to 4% of the population.

1. It is a form of chronic inflammatory process with many possible underlying etiologies including allergy, asthma, infection, cystic fibrosis, and aspirin sensitivity.
2. The main presentations include nasal obstruction, nasal and postnasal discharge, smell disorders and/or headache, and facial pain.

3. There are different lines for treatment of nasal polyposis including medical treatment, surgical treatment, or a combination of both. Systemic and local corticosteroids have good evidence supporting their use as a primary treatment for nasal polyposis or as a postoperative prophylaxis to prevent recurrence.
4. Endoscopic sinus surgery with its major advancement in techniques and equipment has been reserved for cases refractory to medical treatment.⁴ Recurrence of the polyposis is common with severe disease recurring in up to 10% of patients.
5. Omega-3 fatty acids (n-3s) is a class of polyunsaturated fatty acids (PUFAs) having a carbon-carbon double bond located 3 carbons from the methyl end of the chain (compared with omega-6 having this bond 6 carbons from the methyl end).
6. They are present in certain foods such as flaxseed and fish, as well as dietary supplements such as fish oil. They play important roles in the body being components of the phospholipids of the cell membrane with docosahexaenoic acid (DHA), a member of this family, being especially high in the retina, brain, and sperm.⁶ In addition, omega-3s and omega-6s are used by the body to form eicosanoids which are signaling molecules with wide-ranging functions in the body's cardiovascular, pulmonary, immune, and endocrine systems.
7. Many research articles have investigated the potential health benefits for omega-3s with focusing on eicosapentaenoic acid (EPA) and DHA from foods (eg, fish) and/or dietary supplements (eg, fish oil) as opposed to alpha-linolenic acid (ALA) from plant-based foods. Omega-3 fatty acids have well-documented antiinflammatory properties, and consequently therapeutic potential in chronic inflammatory diseases through alterations in the function of inflammatory cells, most importantly endothelial cells and leukocytes.
8. Strong evidence supports the therapeutic role of n-3 PUFAs as a dietary supplement in certain diseases such as rheumatoid arthritis; with other diseases such as asthma and inflammatory bowel diseases being with less supporting evidence.
9. The aim of this study is to assess the potential role of omega-3 supplementation in the medical treatment of nasal polyposis.

PATIENTS AND METHODS

This study is a single-blinded randomized controlled clinical trial (RCT) conducted on recruited patients from the outpatient clinics of Al-Ain, specialized medical care hospital, Al-Ain, UAE, and Zulekha Hospital LLC, Sharjah, UAE, during the period from May 2016 to May 2019. Approval of the ethical committee of each hospital was taken, and a written consent was obtained from every patient before participation in the study.

Patients with grade II nasal polyposis (irrespective to the etiology) according to Lund Kennedy scoring system, which is defined as polyposis extending into the nasal cavity, were included in the study. Any patient with history of recent course of systemic corticosteroids within the previous 3 months and patients with previous history of intranasal surgery for nasal polyposis were excluded from the study. Contraindications for the use of systemic corticosteroids excluded patients also from our study.

According to the previous inclusion and exclusion criteria, 212 patients were initially included in the study. All patients received a course of systemic corticosteroids in the form of 25 mg prednisolone per day for 2 weeks. Local corticosteroids in the form of budesonide/64 mg per puff were prescribed for every patient in a dose of 2 puffs for each nostril twice daily. A second endoscopic assessment of the patients was performed at the end of the previous course of treatment.

Any patient with residual nasal polyposis was excluded from the study. In turn, eligible patients for our study were 164 patients who got randomly distributed among 2 equal groups utilizing block randomization method using 4 blocks each comprising 4 patients with 6 patterns for every block one of which was selected randomly using random numbers generated by Excel program.

Group I included 82 patients who received FDAapproved omega-3 in the form of OmacorVR 1000 mg omega-3-acid ethyl esters 90 (including EPA and DHA; Manufactured by Banner Pharmacaps Europe B.V., the Netherlands, for Abbott Laboratories GmbH, Hannover, Germany) in a dose of 1g thrice daily with meals and budesonide (64 mg per puff in a dose of 1 puff for each nostril twice daily). Group II included 82 patients who received budesonide (64 mg per puff in a dose of 1 puff for each nostril twice daily).

The author was blinded to the clinical progress of each patient within both groups as the senior resident, who is already blinded to treatment protocol, was invited to perform the routine follow-up nasal endoscopic assessment of each patient in the study and to record those endoscopic findings to be collected and statistically analyzed by the author at a later point. Figure 1 shows the RCT flowchart for this study.

All patients were followed up every month for 1 year using endoscopic assessment together with recording of any side effects that might occur from the medication. Patients were instructed to visit the hospital at the first onset of hyposmia irrespective of their scheduled follow-up visits.

OUTCOMES

Primary outcomes include comparison between the 2 groups regarding the number and percentage of patients having recurrent nasal polyposis. Secondary outcomes include comparison between the 2 groups regarding the duration from starting maintenance treatment to onset of recurrent polyposis and the grade of recurrent polyposis assessed at the end of 1 year followup to standardize the point of evaluation for all patients without changing the protocol of treatment even after the first evidence of recurrence. Also any possible side effects from the drug were assessed.

STATISTICAL ANALYSIS

Data were collected, tabulated, and statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 22, IBM Corp, Armonk, NY, USA. Descriptive statistics for quantitative data presented as mean (X) and standard

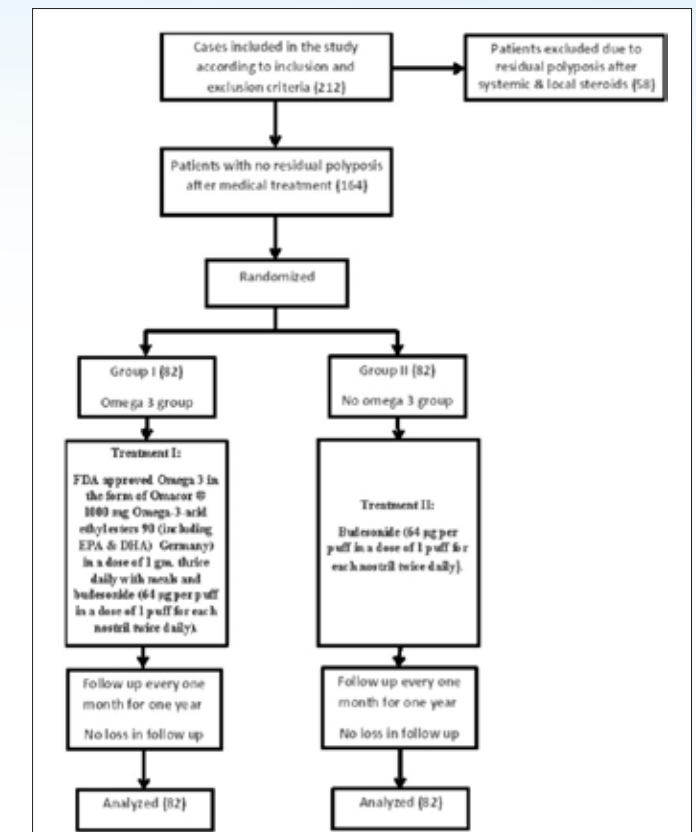


Figure 1. Randomized controlled trial flowchart for the study. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration.

deviation (SD). Qualitative data presented as numbers and percentages (%). Data turned up to be nonnormally distributed according to Kolmogorov-Smirnov test. Mann Whitney U test was used to compare quantitative data of both groups. Chi-squared test (χ^2) was used to study association between 2 qualitative variables. Kaplan Meier survival analysis was performed to compare the duration to recurrence between the 2 groups with weekly time points and recurrence of sinonasal polyposis being the target event. Log rank test was used to calculate the significance level between the survival (recurrence) durations between the 2 groups. Two-sided P value of .05 was considered statistically significant, while 2-sided P value of (.001) was considered statistically highly significant.

RESULTS

This study included 164 patients distributed equally between 2 groups. Group I included 82 patients with 55 males and 27 females and an age of 34.95 $\pm$ 5.86 years. Group II included 64 males and 18 females and an age of 33.57 $\pm$ 5.84 years. There was a nonsignificant difference between the 2 groups regarding age and sex ($P=0.11$ and $P=0.12$, respectively; Table 1). In this study, there was a nonsignificant difference between the 2 groups regarding incidence and grade of recurrence of nasal polyposis ($P=0.1$ and $P=0.66$, respectively). However, there was a highly significant difference between the 2 groups regarding the duration from starting maintenance treatment to onset of recurrent polyposis ($P<0.0001$) favoring group I (Table 2). Kaplan Meier

Table 1. Demographic Data of Both Study Groups.

Item	Omega-3 Group (82)	No Omega-3 Group (82)	Statistical Test	P
Age(mean SD)Sex	34.95±5.86	33.57±5.84	Z=1.61644	.11
Male, n (%)	55 (67.07%)	64 (78.05%)	Chi=2.480	.12
Female, n (%)	27 (32.93%)	18 (21.95%)		

Abbreviations: Chi, χ^2 test; Z, Z value of Mann Whitney U test.

Table 2. Comparison Between the 2 Groups Regarding Recurrence of Nasal Polyposis and Duration From Starting Maintenance Treatment to Onset of Recurrence of Polyposis and Grade of Recurrent Polyposis.

	Omega-3 Group (82)	No Omega-3 Group (82)	Statistical Test	P
Recurrence of polyposis				
Yes	49 (59.8%)	59 (72%)	Chi=2.7116	.1
No	33 (40.2%)	23 (28%)		
Duration for recurrence (weeks), mean SD	37.1±4.16	16.29±3.87	Z= -8.91705	<.00001
Grade of polyposis				
1st	27	30	Chi=0.1944	.659263
2nd	22	29		

Abbreviations: Chi, χ^2 test; Z, Z value of Mann Whitney U test.

Table 3. Means and Medians for Recurrence Time Based on Kaplan Meier Survival Analysis.

Mean					Median				P Value Log Rank (Mantel-Cox)
95% Confidence Interval					95% Confidence Interval				
Group	Estimate	Standard Error	Lower Bound	Upper Bound	Estimate	Standard Error	Lower Bound	Upper Bound	
Omega-3 group	43.098	.880	41.372	44.823	41.000	1.234	38.580	43.420	.000
No Omega-3 group	26.305	1.808	22.762	29.848	18.000	1.207	15.634	20.366	
Overall	34.701	1.200	32.349	37.054	37.000	1.524	34.013	39.987	

survival analysis curve demonstrated such difference between the 2 groups with a highly significant difference between the 2 groups (P<.000; Table 3, Figure 2). Eight patients out of 82 patients in group I (9.8%) experienced side effects with the use of omega-3 in the form of mild gastrointestinal tract (GIT) discomfort.

DISCUSSION

Chronic rhinosinusitis with nasal polyposis is a complex inflammatory process with many factors contributing to its pathogenesis. It is mainly attributed to defects in the innate immunity of the airway epithelium with diminished expression of antimicrobial molecules and diminished barrier function. This facilitates colonization by fungi and bacteria with development of chronic inflammation mediated by many inflammatory cytokines and chemokines, including IL-5, thymic stromal lymphopoietin, and CCL11. Together, these factors likely combine to drive the influx of a variety of immune cells, including eosinophils, mast cells, group 2 innate lymphoid cells, and lymphocytes, which participate in the chronic inflammatory response within the nasal polyps.¹⁰ Treatment of nasal polyposis involves several modalities including medical or surgical treatment by endoscopic sinus surgery with a general aim of elimination or reduction of the size of the polyps causing improvement of nasal symptoms including nasal obstruction, nasal and postnasal discharge, and olfaction and taste disorders.

In general, medical treatment is considered as a primary modality with surgical treatment reserved for patients resistant to medical treatment.¹¹ With both treatments, recurrences are common, particularly in patients with asthma who are twice as likely to develop recurrence compared with nonasthmatics.¹²

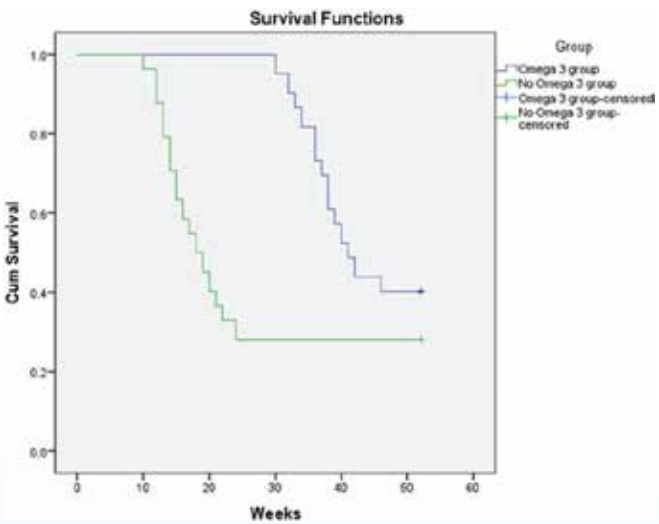


Figure 2. Kaplan Meier survival analysis curve for comparison of duration to recurrence between the 2 groups.

Corticosteroids (either topical or systemic) represent the key element in medical treatment of nasal polyposis. Topical corticosteroids have improved the treatment of nasal polyposis by a combination of their antiinflammatory effects and their ability to reduce airway eosinophilic infiltration¹³ Short-term systemic steroids are reserved for advanced or refractory cases particularly when allergy is present. Long-term systemic treatment should be avoided due to steroid side effects.¹⁴ The adverse effects of long-term systemic steroid use include glucose intolerance, hypertension, adrenal suppression, gastrointestinal bleeding, and altered mental state. So it is important that following short-term systemic steroid, therapy should be maintained with topical steroids especially aqueous nasal sprays.¹⁵

In this study, we have evaluated the potential role for omega-3 through its anti-inflammatory actions in the medical treatment of nasal polyposis in a trial to minimize the need for systemic steroid administration with its consequent adverse effects. We have found a nonsignificant effect for omega-3 on the incidence of recurrence of nasal polyposis or the grade of recurrent polyposis. However, omega-3 intake has a highly significant effect on delaying the incidence of recurrence of polyposis and therefore delaying the need for systemic steroid administration.

The proposed anti-inflammatory mechanism of action of omega-3 has been described by Calder¹⁶ who stated that EPA and DHA fatty acids are capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, as well as production of prostaglandins, leukotrienes, and proinflammatory cytokines. EPA and DHA give rise to anti-inflammatory and inflammation resolving mediators called resolvins, protectins, and maresins. Other mechanisms underlying the anti-inflammatory actions of EPA and DHA include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor that reduces the expression of inflammatory genes, and activation of the antiinflammatory transcription factor peroxisome proliferator-activated receptor.

Previous studies have evaluated the antiinflammatory role of omega-3 intake in the management of several inflammatory diseases including rheumatoid arthritis, stabilizing advanced atherosclerotic plaques, inflammatory bowel disease, and bronchial asthma. Some studies evaluated such role of omega-3 in the management of diseases of the respiratory mucosa. Saedisomeolia et al.¹⁷ studied the role of EPA and DHA in reduction of release of inflammatory mediators from airway epithelial cells infected with rhinovirus (RV). Airway epithelial cells were incubated with EPA, DHA, and arachidonic acid for 24 hours, followed by RV infection for 48 hours. They found that DHA resulted in a significant 16% reduction in IL-6 release after RV-43 infection, 29% reduction in IL-6 release after RV-1B infection, 28% reduction in IP-10 release after RV-43 infection, and 23% reduction in IP-10 release after RV-1B infection. It was concluded that DHA has a potential role in suppressing RVinduced airway inflammation.

Miyata and Arita¹⁸ reviewed the role of omega-3 fatty acids and their metabolites in asthma and allergic diseases. They reported that epidemiological and observational studies strongly supported the efficacy of omega-3 fatty acids in the prevention or amelioration of asthma and allergic diseases. Underlying molecular mechanisms have been revealed in part by the identification of fatty acid bioactive metabolites generated via lipoxygenase and cyclooxygenase

pathways, the specialized proresolving mediators that possess anti-inflammatory properties, offering a more precise understanding of these benefits in inflammatory responses in asthma.

Schneider et al.¹⁹ evaluated the role of high omega-3/ low omega-6 diet for the treatment of aspirinexacerbated respiratory disease (AERD) in a prospective pilot trial. They found that such diet may be an appropriate adjunct treatment option for patients with AERD. They reported that this dietary intervention changed cellular fatty acid composition sufficiently to provide for a measurable reduction in both LTE4 and PGD-M, 2 arachidonic acid-derived inflammatory lipids relevant in AERD, while maintaining unchanged levels of the metabolite of PGE2, which may be protective in the disease.

Laidlaw²⁰ reviewed the most recent clinical updates in the evaluation and treatment of patients with AERD. He found a diet that is high in omega-3 fatty acids and low in omega-6 fatty acids can reduce the production of the inflammatory leukotriene and prostaglandin D2 lipids and help improve symptoms for patients with AERD.

Typical intakes of marine n-3 PUFAs are tens to low hundreds of mg per day even in people consuming lean fish or taking standard fish oil capsules.^{21,22} The Food and Agriculture Organization/World Health Organization recently made a recommendation for adults of at least 0.25 g EPApDHA/day.²³ a recommended intake was mirrored by the European Food Safety Authority.²⁴ Such intakes can be achieved by regular consumption of oily fish or by use of fish oil supplements. However, most studies that report effects of marine n-3 PUFAS on inflammatory cell functions or inflammatory mediator production or concentrations have typically used intakes of EPApDHA >2 g per day, equivalent to about 30 mg per kg body weight per day.²⁵ To meet such high dose, regular dietary intake of fish oil or standard fish oil capsules would not be sufficient, hence the need for pharmaceutical preparation with high concentration of EPA and DHA, namely, OmacorVR 1000 mg omega-3-acid ethyl esters 90 in our study.

Commonly reported side effects of omega-3 supplements are usually mild. These include unpleasant taste, bad breath, heartburn, nausea, gastrointestinal discomfort, diarrhea, headache, and odoriferous sweat.²⁶ In this study, only 8 patients in omega-3 group (9.8%) experienced side effects in the form of mild GIT discomfort. This low incidence of gastrointestinal side effects could be attributed to its intake with meals minimizing its effect on gastrointestinal tract.

In this study, we only used an FDA approved omega- 3 (Omacor) to avoid the use of any other nonapproved omega-3 pharmaceutical preparations without the extraction of heavy metals (commonly present in fish) which has its bad impact on human health, specially developing embryos, upon prolonged exposure.

The limitations of our study included that it did not consider the etiology of nasal polyposis as an important variable in assessing the therapeutic response of omega- 3. In addition, further larger studies are needed to confirm our findings with consideration to different dietary habits in different regions all over the globe. We recommend that the health insurance companies will consider covering the costs of omega-3 fatty acids as an essential supplement for cases with nasal polyposis similar to what they do with cases of mixed hyperlipidemias. This is necessary to minimize the financial burden on the patient due to the high cost of the drug with prolonged intake as a maintenance therapy.

CONCLUSION

Omega-3 PUFA has a beneficial effect on delaying the incidence of recurrence of nasal polyposis through its proven anti-inflammatory mechanism of action. This minimizes the need for systemic steroid administration with its known side effects. Omega-3 fatty acids supplementation should be considered while tailoring the maintenance regimen for medical treatment of chronic rhinosinusitis with nasal polyposis.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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REFERENCES

1. Hedman J, Kaprio J, Poussa T, et al. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol*. 1999;28:717–722.
2. Drake-Lee AB. Nasal polyps. *Hosp Med*. 2004;65:264–267.
3. Drake-Lee AB. Nasal polyps. In: Kerr AG, Mackay AS, Bull TR, eds. *Scott-Brown's Otolaryngology*. 6th ed. Vol. 4: Rhinology. Oxford, England: Butterworth- Heinemann; 1997.
4. Hopkins C. Chronic rhinosinusitis with nasal polyps. *N Engl J Med*. 2019;381(1):55–63.
5. Newton JR, Ah-See KW. A review of nasal polyposis. *Ther Clin Risk Manag*. 2008;4(2):507–512.
6. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington, DC: National Academy Press; 2005.
7. Jones PJH, Rideout T. Lipids, sterols, and their metabolites. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. *Modern Nutrition in Health and Disease*. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2014.
8. Harris WS. Omega-3 fatty acids. In: Coates PM, Betz JM, Blackman MR, et al., eds. *Encyclopedia of Dietary Supplements*. 2nd ed. New York, NY: Informa Healthcare; 2010:577–586.
9. Yates CM, Calder PC, Ed Rainger G. Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacol Ther*. 2014;141(3):272–282.
10. Hulse KE, Stevens WW, Tan BK, Schleimer RP. Pathogenesis of nasal polyposis. *Clin Exp Allergy*. 2015;45(2):328–346.
11. Mygind N. Advances in medical treatment of nasal polyps. *Allergy*. 1999;54:12–16.
12. Dinis PB, Gomes A. Sinusitis and asthma; how do they interrelate in sinus surgery? *Am J Rhinol*. 1997;11:421–428.
13. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps group. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. *Rhinology*. 2007;45:97–101.
14. Burgel PR, Cardell LO, Ueki IF, Nadel JA. Intranasal steroids decrease eosinophils but not mucous expression in nasal polyps. *Eur Resp J*. 2004;24:594–600.
15. Bateman ND, Fahy C, Woolford TJ. Nasal polyps: still more questions than answers. *J Laryngol Otol*. 2003;117:1–9.
16. Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. *Biochem Soc Trans*. 2017;45(5):1105–1115.
17. Saedisomeolia A, Wood LG, Garg ML, Gibson PG, Wark PA. Anti-inflammatory effects of long-chain n-3 PUFA in rhinovirus-infected cultured airway epithelial cells. *Br J Nutr*. 2009;101(4):533–540.
18. Miyata J, Arita M. Role of omega-3 fatty acids and their metabolites in asthma and allergic diseases. *Allergol Int*. 2015;64(1):27–34.
19. Schneider TR, Johns CB, Palumbo ML, Murphy KC, Cahill KN, Laidlaw TM. Dietary fatty acid modification for the treatment of aspirin-exacerbated respiratory disease: a prospective pilot trial. *J Allergy Clin Immunol Pract*. 2018;6(3):825–831.
20. Laidlaw TM. Clinical updates in aspirin-exacerbated respiratory disease. *Allergy Asthma Proc*. 2019;40(1):4–6.
21. British Nutrition Foundation. Briefing Paper: N-3 Fatty Acids and Health. London, England: British Nutrition Foundation; 1999.
22. Meyer BJ, Mann NJ, Lewis JL, Milligan GC, Sinclair AJ, Howe PR. Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids*. 2003;38:391–398.
23. Food and Agriculture Organization of the United Nations. *Fats and Fatty Acids in Human Nutrition: Report of an Expert Consultation*. Rome, Italy: FAO; 2010.
24. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific Opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids, trans fatty acids, and cholesterol. *EFSA J*. 2010;8:1461.
25. Calder PC. The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins Leukot Essent Fatty Acids*. 2008;79:101–108.
26. Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging*. 2012;33:1482.e17–1482.e29.

5-FU INDUCED LEUKOENCEPHALOPATHY IN A PATIENT WITH METASTATIC COLORECTAL CANCER

A case study by Alexis Hospital, Nagpur



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ABSTRACT

Patients with reduced Dihydropyrimidine Dehydrogenase (DPD) activity are at risk for experiencing serious adverse effects following 5-Fluorouracil (5-FU) based chemotherapy. Neurotoxicity is considered an extremely rare side effect of 5-FU. We report here on an unusual case of 5-FU induced encephalopathy. A 62-year-old gentleman with metastatic colorectal carcinoma was treated with palliative chemotherapy with FOLFIRI/Cetuximab that consisted of infused 5-FU (1,200 mg/m²) for 2 days, Cetuximab, Irinotecan and Leucovorin on day 1. Two days after chemotherapy, the patient displayed a sudden onset of slurred speech, confusion, cognitive disturbances and paranoia. A Magnetic Resonance Image (MRI) of the brain showed a diffusion-restricted lesion in the splenium of the corpus callosum. The patient was treated with a hydration and thiamine infusion, and his symptoms then recovered after 2 days. The prognosis of this toxic effects of 5-FU is usually good if recognized and treated in time. General Practitioners and Oncologists should be aware of these rare side effects of 5-FU chemotherapy and its diagnosis and treatment.

Keywords: 5-FU, Neurotoxicity, Encephalopathy

BACKGROUND

5-Fluorouracil (5-FU), a commonly used antimetabolite and antineoplastic agent, has been approved for treatment of various cancers. Common adverse effects of 5-FU therapy include myelosuppression, nausea, vomiting, diarrhea, mucositis and hand-foot syndrome. Acute encephalopathy is a rare neurotoxicity of 5-FU, and only a few case reports have been published in the English literature. 5-FU-induced encephalopathy is often associated with a MRI-identifiable lesion in the brain. The characteristic findings are diffuse and include high-signal intensity in the deep cerebral white matter and corpus callosum on T2-weighted images. We present a case of acute leukoencephalopathy with a unique reversible lesion on the splenium of the corpus callosum in the brain of a patient with colorectal cancer being treated with folinic acid Leucovorin, 5-FU, Irinotecan (FOLFIRI) plus Cetuximab.

CASE PRESENTATION

A 62-year-old gentleman with a history of stage IV colorectal cancer presented to the emergency department (ED) with confusion, dysarthria and agitation. A family member reported that the patient had begun to exhibit intermittent confusion and dysarthria the previous evening. The patient was profoundly confused, agitated, dysarthric and ataxic the following morning and was brought to the ED. There was no history of fever, head injury, previous or current witnessed seizure, smoking or use of alcohol or illicit drugs. Nausea and vomiting were reported to have occurred intermittently since the start of

chemotherapy. The patient had a medical history of diabetes mellitus, metastatic colorectal cancer with no evidence of brain metastasis, and hypertension. The patient's medication list included Metformin, Ondansetron and Pantaprazole.

The patient had been diagnosed 14 months previously with colorectal adenocarcinoma. After having received four cycles of CAPE-OX, he was on regular follow up for 9 months when he developed liver metastases; the patient was started on FOLFIRI/Cetuximab with evidence of disease progression. Two days before presenting to the ED, the patient received his sixth cycle of Leucovorin 400mg/m², 5-FU 400mg/m², Irinotecan 180mg/m² and Cetuximab 500mg. He then underwent a 46-hour continuous infusion of 5-FU 2400mg/m. The patient presented to the ED 3 hours after completing this continuous 5-FU infusion.

INVESTIGATIONS

In the ED, the patient's triage vitals were heart rate 106 beats/min, respiratory rate 18 breaths/min, blood pressure 100/82mm Hg, temperature 98.8°F and oxygen saturation 100% on room air. The patient was confused, dysarthric and highly agitated. He was able to follow simple commands but not able to articulate clearly. Initial blood work showed creatinine 1.0 (normal range 0.7–1.3mg/dL), bilirubin (total bilirubin 0.8 mg/dL (normal range 0.2–1.3mg/dL). Complete blood count, serum electrolytes, glucose, ammonia, blood pH and liver enzyme results were normal except for mild hypokalemia 3.3 mEq/L (normal range 3.5–5.0 mEq/L). Review of his previous investigations revealed that he is having heterozygous mutation in Dihydropyrimidine Dehydrogenase (DPD) gene. Other systemic examination results were within normal range. Chest X-ray and CT head were negative. The patient was admitted to the hospital. Axial sections at the level of lateral ventricles reveal multiple diffuse confluent areas of restricted diffusion in the white matter, corona radiata and corpus callosum.

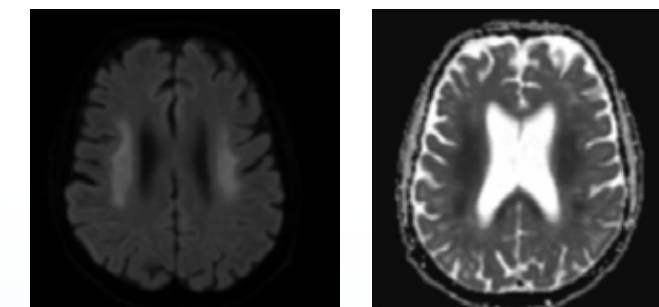


Figure 1: Axial sections at the level of lateral ventricles reveal multiple diffuse confluent areas of restricted diffusion in the white matter, corona radiata and corpus callosum

TREATMENT

He received intravenous hydration, antibiotics and thiamine supplementation during the hospital stay in an attempt to control his symptoms.

OUTCOME AND FOLLOW-UP

The patient's mental status improved to baseline within 24 hours of his presentation to the ED with intravenous hydration and thiamine supplementation. He was discharged home on the fourth day after presentation. Follow-up brain MRI 2 weeks after hospital presentation showed resolution of the previously reported lesion (Figure 2). Subsequently, the patient continued on chemotherapy with Cape-IRI/Cetuximab with 50% dose reduction of capecitabine

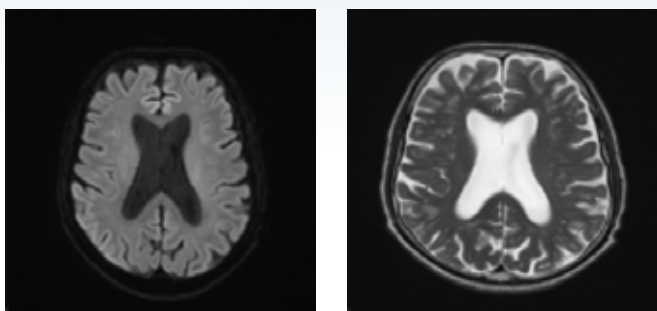


Figure 2: MRI after 10 days of withdrawal of therapy reveals complete resolution of the previous areas of restricted diffusion.

DISCUSSION

5-FU was first synthesized in 1957, and it is currently one of the most widely used anti-cancer, anti-metabolic agents as it shows activity against a broad range of solid tumors, including gastrointestinal, breast and head and neck cancer. The spectrum of 5-FU's toxicities is both dose and schedule-dependent⁽¹⁾. The main effects of this drug are on rapidly dividing tissues, and specifically the gastrointestinal mucosa and bone marrow. Neurotoxicity is one of the rare adverse effects associated with 5-FU treatment. The acute and delayed forms of 5-FU related neurotoxicity have been reported⁽²⁾. The acute form consists of cerebellar syndrome that's characterized by an acute onset and reversibility upon drug discontinuation, as well as encephalopathy, whereas the delayed variety takes the form of subacute multifocal leukoencephalopathy. Although some theories have been proposed, the mechanisms for the neurotoxicity of 5-FU are poorly understood. One such theory to explain the neurologic adverse effect by 5-FU therapy is that this drug brings about a deficiency of thiamine. Thiamine pyrophosphate (TPP) is the active form of the vitamin. Exposure to 5-FU can increase the TPP level. These results indicate that 5-FU may increase the cellular thiamine metabolism, and this can possibly exacerbate thiamine deficiency⁽³⁾. This theory is supported by the fact that the symptoms of the Wernicke-Korsakoff syndrome, including ataxia, nystagmus, mental confusion and cognitive changes, are similar to the neurotoxic effects of fluorouracil.

Dehydropyrimidine Dehydrogenase (DPD) is a breakdown enzyme of 5-FU, and DPD is distributed in the liver, gastrointestinal mucosa and peripheral lymphocytes. More than 80% of the administered 5-FU is catabolized by DPD⁽⁴⁾. Thus, a deficiency of this enzyme can cause life-threatening or fatal toxicity when a patient is treated with fluoropyrimidine based chemotherapy⁽²⁾. The incidence of DPD deficiency in cancer patients has been estimated to be 2.7%, and this malady can be accompanied by severe fluorouracil toxicity⁽⁷⁾ and this was the probable cause in our patient too who has heterozygous

mutation in DPD gene with characteristic symptomatology and radiological findings.

The diagnosis of 5-FU related encephalopathy is one of exclusion: (1) the development of encephalopathy during or shortly after the completion of 5-FU administration, (2) exclusion of other metabolic factors that may affect a patient's consciousness and mental functioning, such as hypoglycemia, organ failure, electrolyte imbalance, sepsis and central nervous system involvement by cancer, and (3) exclusion of an adverse effect by concomitant medications⁽⁸⁾.

In conclusion, physicians should take notice of the neurological symptoms of cancer patients who are being treated with 5-FU-based chemotherapy.

REFERENCES

1. Grem JL. 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. Invest New Drugs. 2000; 18:299–313.
2. Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. Ann Pharmacother. 2000;34:35–38.
3. Koenig H, Patel A. Biochemical basis for Fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. Arch Neurol. 1970; 23:155–160.
4. Kim YA, Chung HC, Choi HJ, Rha SY, Seong JS, Jeung HC. Intermediate dose 5-Fluorouracil-induced encephalopathy. Jpn J Clin Oncol. 2006;36:55–59.
5. Heier MS, Dornish JM. Effect of the fluoropyrimidines 5-Fluorouracil and Doxifluridine on cellular uptake of thiamine. Anticancer Res. 1989;9:1073–1077.
6. Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB. Clinical pharmacokinetics of 5-Fluorouracil and its metabolites in plasma, urine, and bile. Cancer Res. 1987;47:2203–2206.
7. Etienne MC, Lagrange JL, Dassonville O, Fleming R, Thyss A, Renee N, et al. Population study of Dihydropyrimidine Dehydrogenase in cancer patients. J Clin Oncol. 1994;12:2248–2253.
8. Yeh KH, Cheng AL. High-dose 5-Fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. Br J Cancer. 1997;75:464–465.

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR PARA- CARDIAC LUNG METASTASIS FROM HCC

A case study by Alexis Hospital, Nagpur



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ABSTRACT

Lung metastasis from primary tumours of breast, colorectal, ovary, kidney and other organs are a common site for Metastasis. With recent concept of oligo-metastases, which represent a midway state between the spectrum of non-metastatic and disseminated disease, more aggressive treatment of lung metastases in the form of Metastectomy or SBRT has come into picture and is being used very commonly in practice. Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative body radiotherapy (SABR) is a form of high-precision radiotherapy, characterized by the use of extremely high biological doses of radiation delivered in a few fractions, usually between 3 and 8 in a 2-to-3 week period. Metastectomy being a surgical procedure, is an invasive modality, which is usually not suitable in majority of patients due to age, medical comorbidities or poor PS of patients as they are many a times heavily pre-treated with systemic therapy, before being planned for any local treatment. Hence, SBRT has become a common modality in use these days as it is equally effective by delivering high ablative dose of radiotherapy in a very accurate, precise manner with excellent sparing of nearby normal critical organs. Here we present a case of HCC with a solitary central lung metastatic nodule, close to heart, treated with SBRT at Alexis Hospital, with complete response on PET CT with no significant treatment related toxicity.

CASE:

We present case of a 68-year old gentleman with good performance status, who had history of hepatitis in 1997, and consequent cirrhosis, for which he underwent liver transplant in 2017, the histopathology of liver tissue showed evidence of Hepatocellular Carcinoma (HCC). He was on oral TKI for a period of 2 years. He was doing absolutely well, when on routine follow-up Fluoro-deoxyglucose (FDG) whole body PET CT, which showed single low grade FDG avid nodule of size 1.8*1.5cm in left lung, just adjacent to pericardium. Biopsy of this lesion was critical, due to its anatomic location and due to its proximity to heart, it was not suitable for radio-frequency ablation. Hence, patient was planned to be treated based on PET CT report. He was planned for SBRT to this lesion to a dose of 48Gy in 6 fractions, treated over a period of 7 days. It was closely abutting the pericardium, hence was critical to achieve safe dose constraints for heart. Dose parameters received by heart: mean dose 2.39Gy, D1cc:39.5Gy, V5 12.3%. Due to close proximity to heart, it was also important to check for respiratory motion and target it in safest position. Hence we did a planning 4DCT of thorax in free breathing and gross tumour volume (GTV) was delineated by registering PET CT images with planning CT.

An internal target volume (ITV) was created, taking into account the motion of lesion during respiration by using 4DCT data and planning target volume (PTV) was generated by giving 5 mm margin in all directions to account for any set up error. Intrafraction verification was done by on board imaging using kilovoltage Cone Beam CT scan (kVCBCT) just before starting each session and mid-way through the session. He tolerated the treatment well and had an uneventful follow-up period. Response evaluation FDG PET CT done at 3 months showed complete metabolic response in the lesion and no disease elsewhere. He is now 9 months post treatment, doing well with disease controlled and a follow up 2D Echo is being done every 3 monthly to monitor his cardiac function, which is also showing normal ejection fraction values with good cardiac function.

DISCUSSION

Lung metastases can be effectively be treated by SBRT with local control in the range of 70-90% at 2 years. Anatomically, lung lesions are generally classified as central vs peripheral, in reference to its proximity to bronchial tree, and is useful in deciding the prescribing dose of SBRT. However, central lesions are more challenging to treat, as they lie in close proximity to other mediastinal structures also like heart, esophagus and major blood vessels. Hence, a carefully selected dose regimen is to be decided, so as to achieve best local control possible with acceptable treatment related toxicities. RTOG 0813 has described that dose of 10-12Gy per fraction, delivered for 5 fractions is very well tolerated with acceptable late toxicity. However, in this study, there were very few patients in whom, the tumour was approximating organs other than Bronchial tree (e.g heart, esophagus). Also there are no definite constraints for heart defined while treating SBRT for lesions in such proximity to heart or pericardium. We tried to achieve doses with as low as reasonably achievable (ALARA) principle.

Haasbeek et al had reported outcomes of SBRT for primary lung cancers, lesion located close to heart and other critical structures. They had used a regimen of 60Gy in 8 fractions in such cases, cohort of 63 patients was treated, of which 11 were located close to pericardium. There was one death reported from cardiac cause among these 11 patients, who had chronic atrial fibrillation and a pre-treatment severe aortic stenosis.

Hence, our discussed case was an uncommon example, due to its proximity to pericardium and precise delivery of carefully planned SBRT was mandatory, to offer excellent local control, without compromising his quality of life and keep a check on cardiac function.

REFERENCES:

1. Andrea Bezjak, MD; Rebecca Paulus; Laurie E. Gaspar, MD; Robert D, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol 37:, Issue 151316-1325. 2009
2. Cornelis J. A. Haasbeek, MD, PhD, Frank J. Lagerwaard, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan, MRCP, FRCR, PhD. Outcomes of Stereotactic Ablative Radiotherapy for Centrally Located Early-Stage Lung Cancer. J Thorac Oncol. 2011;6: 2036–2043

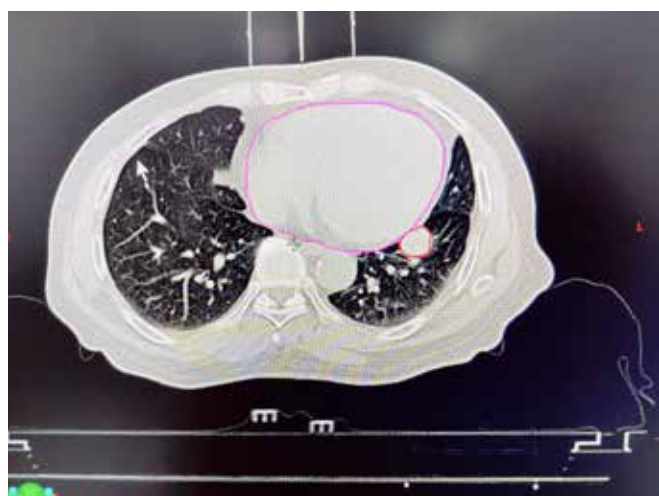


Fig 1: Metastatic nodule in left lung, attached to pericardium

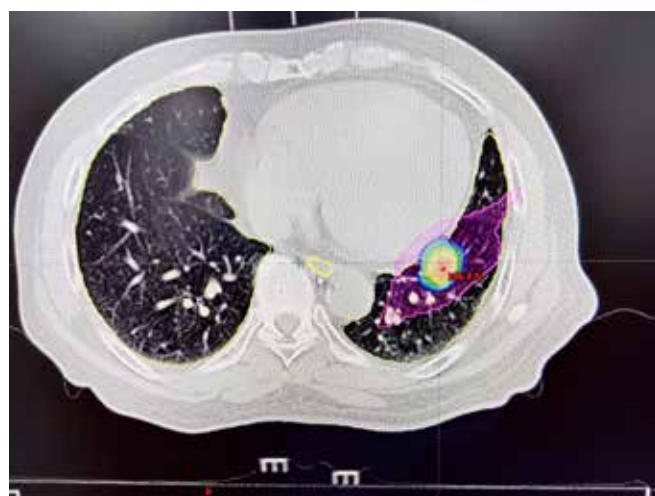


Fig 2: Showing 95% isodose, very well covering the metastatic nodule.

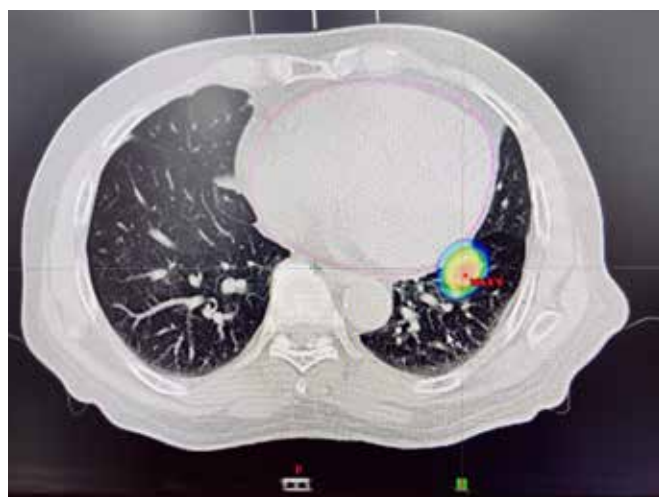


Fig 3: 50% isodose area, showing limited spillage into normal lung parenchyma and cardiac tissue

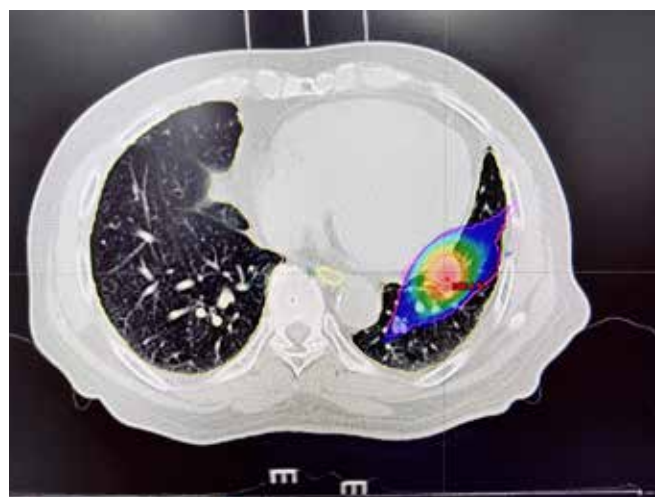


Fig 4: 25% isodose, showing limited spillage into normal lung parenchyma and cardiac tissue

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

A case study by Alexis Hospital, Nagpur



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ABSTRACT

A healthy 12-year-old female developed COVID-19 disease with clinical characteristics resembling Multisystem Inflammatory Syndrome in Children (MIS-C), a rare form of COVID-19 described primarily in children under 21 years of age. She developed this complication after 3 weeks of the infection. She was critically sick and admitted in intensive care unit for a long duration of time, suffered multiple complications and finally survived through this rare disease.

INTRODUCTION

During the course of the coronavirus disease 2019 (COVID-19) pandemic, reports of a new multisystem inflammatory syndrome in children (MIS-C) have been observed. Clinical features in children have varied but predominantly include shock, cardiac dysfunction, abdominal pain, and elevated inflammatory markers, including C-reactive protein (CRP), ferritin, D-dimer, and interleukin ⁶. The mortality rate of MIS-C appears to be low, though severe illness is common, and a number of fatalities in children have been reported.¹

The diagnosis of MIS C includes, An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and No alternative plausible diagnoses; and Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.²

CASE :

GW is a 12-year-old female with history of Covid 19 Infection (20 days back) was brought to the Hospital with high-grade fever, breathlessness and altered sensorium. On examination, was found to be hypoxic, tachypnic, thrombocytopenia (platelet 22000). WBC counts were raised (14730), CRP was 79.5 and serum ferritin 1681. CT thorax was suggestive of areas of consolidation in right lower lobe, with right-sided pleural effusion. Liver functions test showed raised SGOT and SGPT with hypoalbuminemia. INR was increased to 2. CT brain was normal. Procalcitonin level were raised (4.740). Tests for scrub typhus, dengue, and leptospira were negative. Patient was admitted in ICU and was started on NIV support, intravenous steroids and antimicrobials (Meropenem, tecoplanin, and Micafungin).

She was later intubated due to persistent hypoxia. She was transfused with single donor platelet and ultrasound-guided pleural tapping (500 ml) was done. Pleural fluid analysis showed 50% polymorphs, 20% lymphocytes. Her blood culture showed growth *Candida Parapsilosis*. In ICU, patient had an episode of bradycardia and chest pain and hypotension requiring inotropic support. Trop-T and NT-pro BNP both were elevated however an echocardiogram was normal. She then developed convulsions and on further investigations found to have hypocalcemia and hypokalemia.

These dyselctrolytemia was severe and prolonged (7days). She was gradually weaned off from inotropes and ventilatory support. After shifting from ICU, she had weakness in all 4 limbs and was not able to walk however nerve conduction study could not demonstrate any abnormality. With physio support she improved, could walk without support in next few days. She was discharged home on day 21 of hospitalization

DISCUSSION

This patient developed high grade fever and breathlessness in 3rd week of infection which was unusual since most covid pneumonia occurs between 7-14 days. She did not have classical ground glass opacities on imaging- instead she has consolidation and pleural effusions on both the side. She initially developed pancytopenia and persistent thrombocytopenia. (haematological abnormality). She also developed cardiac dysfunction³ and neurological abnormalities subsequently. We could not understand why she suddenly developed severe and refractory dyselctrolytemia during her course. This probably can be one of the presentation of MIS C .

Before she was admitted at our hospital, she was admitted elsewhere for brief duration and received intravenous methyl prednisone 1 mg/ kg body weight. She had candidemia at the same time. This is rather a uncommon finding in patients of this age with modest doses of methyl prednisone without any other immunosuppressive conditions.⁴

Proposed mechanisms for extrapulmonary dysfunction in COVID-19 include endothelial damage and thromboinflammation, dysregulated immune responses, and dysregulation of the renin-angiotensin-aldosterone system⁷ Recent literature also indicate the role of autoantibodies (against interferons and other cytokines) which is responsible for severe extrapulmonary manifestations.⁸ Given the high proportion of MIS-C patients with negative PCR testing, clinical guidelines recommend the use of both antibody and viral testing to assist with diagnosis.⁵

CONCLUSION

Multisystem Inflammatory Syndrome in Children (MIS-C), a rare form of COVID-19 which has atypical presentation. Establishing a diagnosis is difficult due to many other overlapping features and absence of classical covid symptoms. Careful history taking, measuring covid antibodies when in doubt and managing this patients carefully can result into excellent outcomes. Refractory cases can be managed with administration of intravenous immunoglobulin.⁶

REFERENCES

1. World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance>
2. Centers for Disease Control and Prevention. 2019 Novel coronavirus, Wuhan, China. Information for Healthcare Professionals. <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html>
3. Belhadj Z, Méot M, Bajolle F, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation* 2020; 142:429.
4. Kaushik A, Gupta S, Sood M, et al. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. *Pediatr Infect Dis J* 2020; 39:e340.
5. Paediatric Intensive Care Society (PICS) Statement: Increased number of reported cases of novel presentation of multi system inflammatory disease. Available at <https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf>
6. Health Alert Network (HAN): Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). <https://emergency.cdc.gov/han/2020/han00432.asp>
7. Licciardi F, Pruccoli G, Denina M, et al. SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children. *Pediatrics* 2020; 146.
8. Whittaker E, Bamford A, Kenny J, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. *JAMA* 2020; 324:259.



Figure 1: Inflammatory Infiltrate



Figure 2: Massive effusion on both sides

PREGNANCY WITH UNDIAGNOSED SLE AND HELLP SYNDROME

A case study by Alexis Hospital, Nagpur



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ABSTRACT

Systemic lupus erythematous is an autoimmune disease that primarily appears in women in their childbearing age. The peak incidence is between 15 and 40 years with a female to male ratio of 9 to 1. SLE is diagnosed through combination of signs, symptoms and laboratory findings. The course of SLE both during and outside pregnancy can be unpredictable. Some women will have significant fatigue and arthralgia without maternal organ damage. Others may have fulminant course with rapid progression to end stage renal disease. We present a case of 32-year-old female with undiagnosed SLE with secondary thrombocytopenia and her stormy course throughout pregnancy and delivery.

INTRODUCTION

SLE is basically a multisystem disorder, which can present with myriad of symptoms, many of which are non-specific. The most common symptoms include fatigue, arthralgias, especially in the small joints of hands, rashes, low-grade fever, Raynaud's phenomenon and hair loss. Accordingly, the criteria developed by American College of Rheumatology (ACR) a woman must have at least four of 11 criteria to be labelled as lupus. Over 95% of women with SLE will have a positive antinuclear antibody. Other antibodies including Anti-ds DNA, RO/LA, RNP and Smith antibodies are not required for SLE diagnosis, but are helpful when present.¹

The ANA is the classic autoantibody associated with SLE. Once a high titre ANA has been identified (i.e. 1:320) there is no reason to repeat the test. The double standard DNA and anti smith antibodies are unique to lupus. The ds DNA antibody titre can increase with disease activity and hence frequently monitored in patient with SLE. The RO and LA antibodies are important in pregnancy because they can cause neonatal lupus.³

A significant minority of women with SLE will have hematologic abnormalities. Thrombocytopenia is the most common abnormality. This case highlights the importance of step-wise approach for the thorough evaluation and treatment of a patient with SLE². Also it depicts role of multidisciplinary care approach for achieving excellent maternal and foetal outcome.

CASE REPORT

A 31-year-old female married life of 7 years Gravida 2 Para 1 living 1 came to our hospital at the gestational age of 12 weeks. She was referred from another hospital as her platelet counts were just 35000. On thorough history taking, she had thrombocytopenia in previous pregnancy also, had normal delivery and history of post partum haemorrhage 3 days after normal delivery. She had received multiple blood and blood products and then recovered. She was discharged on day 10 of delivery. Further evaluation was not done. She never checked her hemogram after that. This pregnancy,

she came to Alexis hospital with platelet count of 35000. On through history, patient had complains of arthralgia involving small joints of hands and feet.

On examination, rashes over trunk were noticed. On further evaluation, ANA returned positive, Anti-DS DNA was positive, RO, LA positive, C3- C4 was negative. So a diagnosis of SLE with secondary thrombocytopenia was made. She was started on oral steroids in variable doses. Her platelet count continued to be low inspite of increase in dose of steroids. Patient was thoroughly monitored throughout pregnancy. Each trimester C3, C4 was done to see for disease activity. Patient was asked to keep home blood pressure record as these patients have risk of pregnancy induced hypertension. Fetal scan was done from 16 weeks onward to monitor PR interval as RO/LA was positive and they have a risk of congenital heart block⁴. Patient started developing late onset IUGR from 28 weeks onward, so growth was closely monitored. At 34 weeks of gestation, Doppler report showed absent umbilical flow and few loops showed reverse end diastolic flow so decision to deliver the baby was taken.

On the day of admission, patient developed blood pressure of 170/100 with severe headache and proteinuria 1+ and platelet count of just 7000 suggestive of HELLP syndrome. Blood report showed haemoglobin 11 and elevated liver enzymes. NST showed deceleration, so we decided to deliver her with SDP support ; 3 units of single donor platelets – 1 pre-op, 1 intra-op and 1 post op. She delivered (emergency LSCS) a preterm male baby weighing 2 kg, baby cried well immediately after birth and handed over to paediatrician. Intraperitoneal and subcutaneous drains were kept in view of thrombocytopenia. Patient was shifted to ICU for monitoring. Drain output was thoroughly monitored and patient was observed for any signs of active bleeding.

Postoperatively patient developed sepsis due to long term steroid administration which was managed by ICU team and ID physician. After stabilisation patient was shifted to ward and discharged after satisfactory recovery. She now continues her follow up with rheumatologist.

DISCUSSION

We thoroughly monitored this patient for flare, lupus nephritis, pre eclampsia and HELLP syndrome during pregnancy. She was also monitored for lupus disease activity by measuring CRP, Platelets, C3-C4 levels and clinical symptoms. Platelets always remained low (< 30000) during pregnancy accompanied by episodes of minor bleeding and hence requiring higher doses of steroids frequently.

Lupus nephritis was monitored by serial monitoring of serum creatinine and urine routine.⁵ We kept an eye on complications like

pre eclampsia by measuring serial weight gain, home blood pressure monitoring, proteinuria, liver function tests and renal function tests. Fortunately although patient was anti Ro, and LA positive, neonate didn't develop feature of lupus. Even after careful watch she developed HELLP syndrome. However due to intense monitoring, we could prevent multiple other complications like bleeding episodes, nephritis, severe IUGR, and Infections.

CONCLUSION

SLE is a multisystem organ disorder having a risk of flare in pregnancy unlike other autoimmune disorder. This flare can manifest with non specific clinical and laboratory abnormalities and can have adverse maternal and fetal outcome if not managed in time.

REFERENCES

1. Clowse ME, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol.* 2008;199(2):127, e121–126.
2. Bramham K, Hunt BJ, Bewley S, Germain S, Calatayud I, Khamashta MA, Nelson-Piercy C. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. *J Rheumatol.* 2011;38(9):1906–1913.
3. Buyon JP, Clancy RM, Friedman DM. Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Clin Pract Rheumatol.* 2009;5(3):139–148.
4. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. *J Am Coll Cardiol.* 2010;55(24):2778–2784
5. [https:// www.uptodate.com/ contents/ pregnancy-in -women -with-systemic-lupus-erythematosus](https://www.uptodate.com/contents/pregnancy-in-women-with-systemic-lupus-erythematosus)

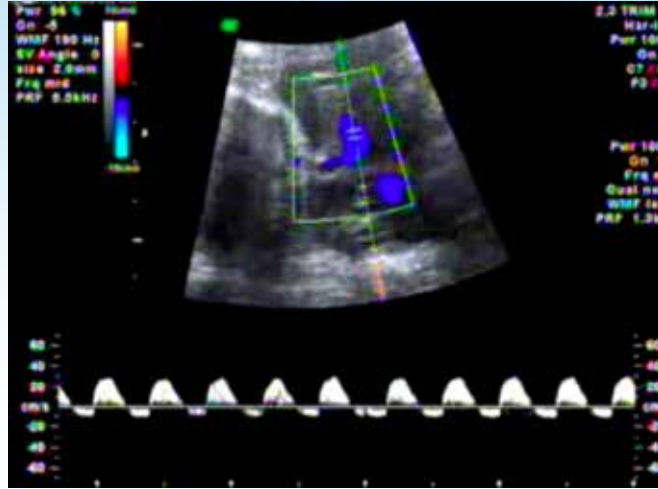


Figure 1: Reverse end diastolic flow in umbilical artery.

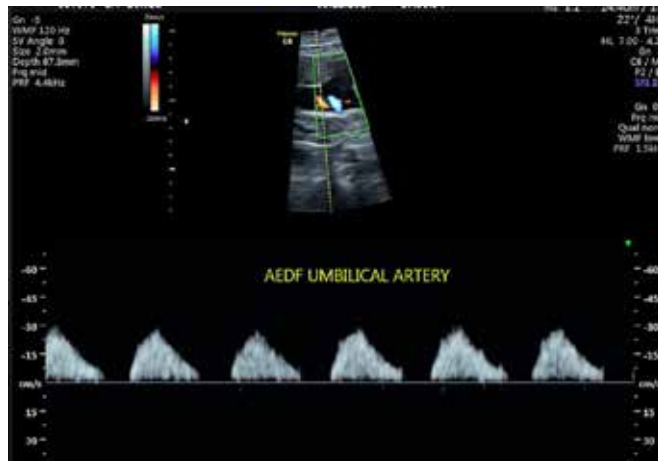


Figure 2: Absent end diastolic flow in umbilical artery.

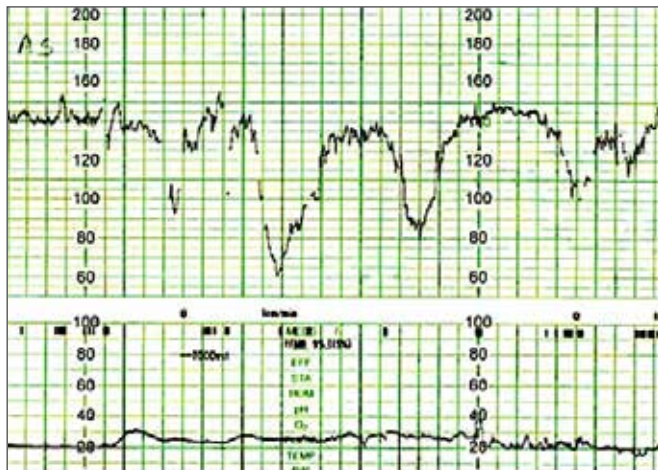


Figure 3: Abnormal non stress test showing type 2 deceleration.

EARLY RECOGNITION OF ACUTE PNEUMONITIS IN AMIODARONE TREATMENT

A case study by Alexis Hospital, Nagpur



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ABSTRACT

Pulmonary complications of long-term amiodarone use are well known. However, acute pneumonitis causing respiratory distress with short-term administration of amiodarone although rare is associated with high mortality. Early diagnosis and treatment with glucocorticoids significantly decrease associated mortality and morbidity. We are reporting one such case of amiodarone-induced pulmonary pneumonitis and its complete resolution with short-course glucocorticoid therapy. Thus, every clinician prescribing amiodarone should be well acquainted with this entity.

Key words: Amiodarone, amiodarone-induced pulmonary toxicity, pneumonitis

INTRODUCTION

Amiodarone, a potent antiarrhythmic, is known to cause pulmonary toxicity. Chronic interstitial pneumonitis is the most common presentation and has been reported in up to 3%–5% of the patients on prolonged amiodarone therapy.^[1] Acute pulmonary toxicity is rare with high mortality rates, and only a few case reports are published till date, so exact incidence is not known.^[2,3] A high index of suspicion facilitates early diagnosis and treatment, thus preventing associated mortality and morbidity. We are reporting one such case of amiodarone-induced acute pneumonitis.

CASE REPORT

A 74-year-old female, with essential hypertension, type-2 diabetes mellitus, and history of mitral valve replacement for calcific mitral stenosis 15 years back, presented with progressive dyspnea for 3 weeks. Dyspnea progressed to the New York Heart Association AQ4 Class 4 for 3 days before presentation. On inquiry, it was revealed that patient was evaluated at 4 weeks back for exertional palpitations and found to have atrial fibrillation with fast ventricular rate and treated with oral amiodarone loading 1200 mg/day for 1 week followed by 400 mg/day maintenance. On examination, the patient was restless and tachypneic (respiratory rate: 37/min). Her oxygen saturation was 79% on room air. Her pulse was 64 beats/min and blood pressure was 144/82 mmHg. Prosthetic valve click was clearly audible. Auscultation of chest revealed diffuse bilateral fine crepitation. Electrocardiogram showed sinus rhythm with prolonged corrected QT (QTc-544 ms). Chest radiogram was suggestive of bilateral diffuse interstitial shadows [Figure 1]. Echocardiography and color Doppler study revealed normally functioning ball and cage prosthetic mitral valve with good left ventricular systolic function. There was severe primary tricuspid regurgitation with no significant pulmonary hypertension. High-resolution computed tomography (HRCT) of chest revealed bilateral diffuse interstitial lung disease

with ground-glass opacities [Figures 2-4]. Biochemical investigations and hemogram were in normal range. Patient was treated with oxygen supplementation, systemic corticosteroids (intravenous hydrocortisone 100 mg tds), and other supportive measures. Amiodarone was discontinued. Over next 5 days, patient

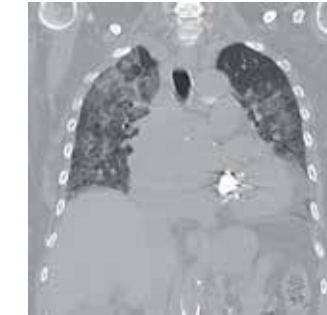


Figure 1: Chest X-ray posteroanterior view showing bilateral interstitial infiltrations



Figure 2: High-resolution computed tomography chest coronal view showing moderate reticular opacities seen in bilateral lung parenchyma with mild interlobular and intralobular septal thickening and mild traction bronchiectasis within and associated with moderate ground-glass opacities

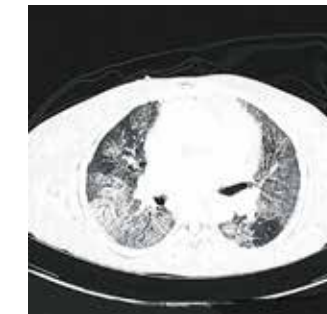


Figure 3: High-resolution computed tomography chest showing diffuse interstitial involvement

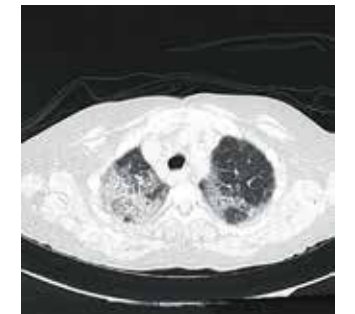


Figure 4: High-resolution computed tomography chest AQ8

improved and achieved oxygen saturation of 95% without oxygen supplementation. Follow-up chest radiogram showed clearing of interstitial shadows [Figure 5]. Thus, the diagnosis of amiodarone-induced acute pneumonitis was made, and patient discharged on short course of oral prednisolone along with anticoagulation, antihypertensive, and insulin therapy.

DISCUSSION

Amiodarone, a potent antiarrhythmic, was first discovered in 1961; however, its use was not approved until 1985 due to significant pulmonary side effects. Occurrence of amiodarone-induced pulmonary toxicity (AIP) varies with patient's age and total accumulated dose. Other risk factors proposed are preexisting lung diseases, treatment duration more than 2 months, ethnicity, and exposure to high concentration of oxygen. The incidence of AIP is reported to be 0.1%–0.5% in patients taking amiodarone 200 mg/day, 5%–15% in patients taking 500 mg/day or more, and in up to 50% of patients taking 1200 mg/day or more.^[3,4] Long-term follow-up studies have shown the occurrence of AIP in as high as 10.6% of patients at 5 years.^[5] Acute pneumonitis is rare and if not diagnosed early is mostly fatal.

Etiopathogenesis of AIP is still controversial; however, there are two main proposed hypotheses, namely direct cytotoxicity and indirect immunological drug hypersensitivity reactions. Amiodarone and its metabolite have direct cytotoxic effect by inducing toxic oxygen radicals and accumulation of phospholipids. Direct cytotoxicity leads to chronic interstitial lung infiltrates and fibrosis.

Acute AIP occurs due to hypersensitivity reaction and infiltration of CD8 T-cells in lung tissue.^[6] AIP has varied clinic-radiological presentation; however, four commonly reported clinical syndromes are as follows:^[6]

- Chronic interstitial lung disease
- Organizational pneumonia with or without bronchiolitis obliterans
- Acute lung injury or acute respiratory distress syndrome
- Pseudomass in upper lobe of lungs.

AIP is a diagnosis of exclusion with no confirmatory laboratory test. However, clinical scenario, history of amiodarone therapy, and typical radiological findings aid in diagnosis. Bronchoscopic-assisted lavage fluid analysis shows lymphocytic infiltration with CD8 lymphocyte predominance. Radiological findings in acute presentation are many a time reversible with complete chest radiogram and HRCT clearing. Pulmonary lung function tests are useful in chronic forms of AIP and show decreased diffusion capacity of lung for carbon monoxide with restrictive pattern.

Management of AIP depends on the clinical presentation. Chronic interstitial form is mostly irreversible and requires discontinuation of amiodarone and supportive management. Acute pneumonitis, although less common, requires a high index of suspicion or early diagnosis and prompt treatment. Amiodarone should be discontinued whenever AIP is suspected. Glucocorticoid therapy in anti-inflammatory doses has been found to be successful in suppressing inflammation and accelerating recovery.^[6] Oxygen supplementation is a double-edged sword in patients with amiodarone toxicity and overenthusiastic oxygenation increases oxygen radical-induced cytotoxicity.

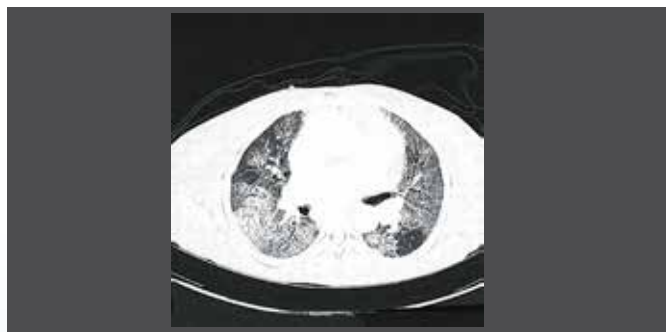


Figure 5: High-resolution computed tomography chest

CONCLUSION

Chronic pulmonary toxicity with amiodarone is well established; however, acute pneumonitis can rarely complicate patient being treated with amiodarone. A high index of suspicion can facilitate early diagnosis and management and prevent fatal outcomes.

REFERENCES

1. Dusman RE, Stanton MS, Miles WM, Klein LS, Zipes DP, Fineberg NS, et al. Clinical features of amiodarone-induced pulmonary toxicity. *Circulation* 1990;82:51-9.
2. Ernawati DF, Stafford L, Hughes FD. Amiodarone-Induced pulmonary toxicity. *BR J Clin Pharmacol*. 2008;66:82-7.
3. Nacca N, Bhamidipati CM, Yuhico LS, Pinnamaneni S, Szombathy T. Severe amiodarone induced pulmonary toxicity. *J Thorac Dis* 2012;4:667-70.
4. Wolkove N, Baltzan M. amiodarone pulmonary toxicity. *Can Respir J* 2009;16:43-8.
5. Yamada Y, Shiga T, Matsuda N, Hagiwara N, Kasanuki H. Incidence and predictors of pulmonary toxicity in Japanese patients receiving low-dose amiodarone. *Circu J* 2007;71:1610-6.
6. Myers JL, Kennedy JL, Plumb VJ. amiodarone lung: Pathologic findings in clinically toxic patients. *Hum Pathol* 1987;18:349-54.

DOUBLE WHAMMY!

A case study by Alexis Hospital, Nagpur



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ABSTRACT

Inflammatory bowel disease (IBD) is associated with a range of extraintestinal manifestations, though their pathogenesis is poorly understood. The elevated risk of thromboembolism (TE) in patients with IBD has been well documented. Patients with IBD have an overall threefold increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism (PE) compared with the general population⁽¹⁾. Cytomegalovirus (CMV) infection is a potentially fatal complication of treatment induced suppression in patient with inflammatory bowel disease (IBD). We present an interesting case of ulcerative colitis where we encountered thromboembolic complication in IBD along with CMV colitis which complicated the management issue in our patient.

Key words - Inflammatory Bowel Disease (IBD), Cytomegalovirus (CMV), Deep Venous Thrombosis (DVT)

CASE REPORT

A 62 years female with known case of ulcerative colitis with history of diabetes mellitus had presented to Gastroenterology clinic with worsening of stool frequency with lower limb swelling. She was diagnosed case of proctosigmoiditis 6 months prior to present hospitalization and she had been on oral mesalamine, azathioprine and topical mesalamine enemas. Colonoscopy done 2 months prior showed moderately active proctosigmoiditis. She had intermittent flares in past requiring systemic steroids. She was hospitalized and started on parenteral steroid, immunomodulators considering flare of ulcerative colitis. Stool toxin assay for *C. Difficile* was negative. CRP was 35 with leukocytosis and mild anemia. On examination she had lower limb swelling with tenderness. Doppler study revealed extensive bilateral deep venous thrombosis (DVT) of lower limb. She was initiated on heparin with targeted INR of 3 and subsequently switched over to warfarin. 3 days later Patient had hypoxia with low oxygen saturation. Considering background history of DVT, CT angiography was done which revealed segmental pulmonary embolism. It was managed with aggressive anticoagulation, oxygen support. During hospitalization on anticoagulation she had significant lower Gastrointestinal (GI) bleed with hypotension for which fresh frozen plasma transfusion along with blood product was administered. To evaluate further, Sigmoidoscopy was done which revealed large, deep geographic and punched out, friable rectal ulcers. Biopsy of same was suggestive of Cytomegalovirus (CMV) Colitis which was confirmed by Immunohistochemistry.

TREATMENT AND FOLLOW-UP

Subsequently she was initiated on IV Ganciclovir, immunomodulatory with tapering dose of steroid. 14 days of treatment with Ganciclovir led to a prompt improvement in the symptoms of Colitis. She responded well to above medical management, there was no further GI bleed during hospitalization. She was subsequently discharged and her repeat sigmoidoscopy at 6 weeks follow up showed significant resolution of Rectal ulcers.

DISCUSSION

Inflammatory Bowel Disease (IBD) is a Chronic Inflammatory condition of Gastrointestinal tract characterised by relapsing and remitting episodes of inflammation which comprised of Ulcerative Colitis and Crohn's disease. During assessment of flare of Ulcerative Colitis (UC), it is pertinent to look for secondary infections like *C. Difficile* and CMV Colitis. CMV infection is not very common in patients with inflammatory bowel disease, where the incidence has been variously reported as 0.5 -3.5%⁽²⁾, although there are several case reports in the worldwide literature mentioning about acute exacerbation of Ulcerative Colitis secondary to CMV infection. Majority of the patients involved are frequently treated with immunosuppressive agents (such as corticosteroids, azathioprine, cyclosporin, or methotrexate) which may increase infection risk. Moreover, gut inflammation itself is considered to be a predisposing factor for infection. The vast majority of cases of CMV infection have been seen in patients with Ulcerative Colitis (UC); rarely seen among Crohn's Disease (CD). Clinical presentation, endoscopic finding, use of serology and parallel PCR analysis to confirm the diagnosis of cytomegalovirus infection should enable early antiviral therapy to be instituted, resulting in marked clinical improvement, as was the case in our patient.

Histology demonstrating the classical appearance of 'Owl's Eye' inclusion bodies is the gold standard test for cytomegalovirus diagnosis⁽³⁾. Our case had classical endoscopic finding of geographic, punched out Colonic Ulcer as seen in CMV colitis which was later confirmed by Immunohistochemistry of the histopathology. It is unusual to have a torrential lower GI bleed in ulcerative colitis that created suspicion for CMV Colitis. Mortality rates for patients with cytomegalovirus enterocolitis have been seen as high as 71%⁽⁴⁾, hence early diagnosis and prompt medical management is warranted among such class of patients. Parenteral therapy with Ganciclovir for 2 weeks is advocated for such patients, steroids needs to be tapered while other immunomodulators can be continued as per the treatment protocol.

Interesting part of our case is, our patient had thromboembolic complication like DVT and Pulmonary embolism which is again a recognised extraintestinal manifestation of Inflammatory Bowel Disease. Ulcerative Colitis has high risk of developing Deep Venous Thrombosis. Ulcerative Colitis has been associated with increased prothrombotic factor VIII activity, elevated fibrinogen levels and accelerated thrombin generation and possibly secondary to inflammation process itself. The current practice in the treatment of VTE for patients with IBD is same as that of patients with non-IBD. Anticoagulation with unfractionated heparin or low molecular weight heparin is recommended, with switched over to oral anticoagulation. Duration of anticoagulation therapy is advocated for 3 months post cessation of flare of Ulcerative Colitis. Considering symptomatic pulmonary embolism with extensive DVT, our patient required long term anticoagulation. However, she was a poor candidate for anticoagulation in view of significant Hematochezia with poorly controlled Ulcerative Colitis with recurrent flare hence IVC filter was placed and simultaneously she was treated for CMV colitis with oral anticoagulant targeting lower INR. After 6 weeks her sigmoidoscopy was done revealed resolving rectal ulcer with no further episodes of Hematochezia. It is not common to have simultaneous complications in a patient of Ulcerative Colitis where CMV Colitis worsened the management of DVT resulting in recurrent lower GI bleed complicating the management of Ulcerative Colitis.

LEARNING POINTS

1. CMV colitis as an important aetiological factor to consider in patients admitted to hospital with an acute exacerbation of Ulcerative Colitis.
2. Pathologist should have high grade of suspicion to look for inclusion body in a specimen of colonic biopsy in a flare of UC.
3. Venous thromboembolism remains an uncommon, although well-documented, extraintestinal manifestation of Inflammatory Bowel Disease (IBD)
4. Flares in IBD itself aggravates the risk of thromboembolism in a patient with an IBD such as UC.

BIBILOGRAPY

1. Bernstein CN, Blanchard JF, Houston Ds, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb haemostat* 2001;85:430–4.
2. Papadakis KA, Tung JK, Binder SW, et al. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001;96:2137–42.
3. Brytting M, Xu W, Wahren B, et al. Cytomegalovirus DNA detection in sera from patients with active cytomegalovirus infection. *J Clin Microbiol* 1992;30:1937–41.
4. Kaufman HS, Kahn AC, Iacobuzio-Donahue C, et al. Cytomegalovirus enterocolitis: clinical associations and outcome. *Dis Colon Rectum* 1999;42:24–30.

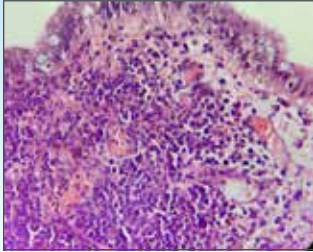


Figure 1: 400X, Section from rectum shows intranuclear inclusions in endothelial cells

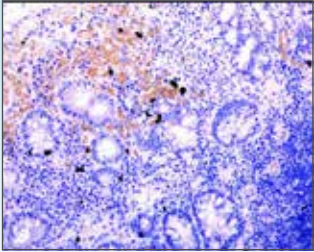


Figure 2: 200x, Immunohistochemistry highlighted the Intranuclear inclusions of CMV infection

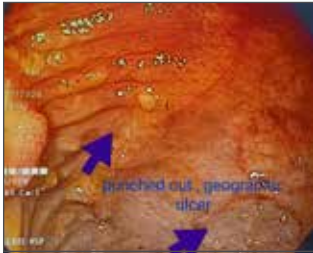


Figure 3: Confluent geographic rectal ulcer



Figure 4: CT Angiography showing Pulmonary Embolism