Case Record Book for MD Medicine Examination

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The masquerades of Eosinophilic granulomatosis with polyangitis : a rare case report of a young male presenting with quadriplegia due to pan CNS vasculitis following appendectomy

Case number : 01

Name of the Consultant : Dr.Upul de Silva

Name of the PGIM trainee : Dr.P.W.G. Chamika

Name of the patient :Mr.V.P.N.Darshana

Age :31 years

Ward number :19

Name of the Hospital :Teaching Hospital Karapitiya

BHT :123152

Date of admission :05.08.2019

Date of discharge :15.08.2019

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Supervising Consultant

The masquerades of Eosinophilic granulomatosis with polyangitis : a rare case report of a young male presenting with quadriplegia due to pan CNS vasculitis following appendectomy

Abstract

Background Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic necrotizing vasculitis affecting small and medium sized vessels. This multisystem disease is typically characterized by 3 phases which include prodromal phase, eosinophilic phase and a vasculitic phase. American College of Rheumatology (ACR), states ≥4/6 criteria are needed for the diagnosis: peripheral eosinophilia (> 10%), paranasal sinusitis, pulmonary infiltrates, histological evidence of vasculitis with extravascular eosinophils, and mononeuritis multiplex or polyneuropathy. Asthma and lung disease are the cardinal clinical features of EGPA. Neurological involvement in EGPA is rare.

Case presentation This is a unique case of a 31 year old patient presenting with bilateral spastic paraparesis with bladder and autonomic involvement, who was initially diagnosed as having transverse myelitis, on the tenth day following an appendectomy, later being diagnosed as having EGPA with CNS vasculitis. This is an atypical presentation of EGPA with CNS, gut and dermatological involvement at the diagnosis without lung or upper airway involvement. ANCA was negative. Remission induced with cyclophosphamide and methylprednisolone pulse therapy. Maintenance therapy was continued with azathioprine.

Conclusion CNS vasculitis due to EGPA is rare. EGPA may not always follow the typical triphasic pattern of the disease. Prompt identification of the disease with atypical presentations and early use of cytotoxic therapy would improve the outcome.

Key words: EGPA, Churg Strauss, CNS vasculitis, Case report, appendectomy, Sri Lanka

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), or traditionally termed Churg Strauss syndrome was first described in 1951 by Churg and Strauss. It is a rare primary systemic necrotizing vasculitis affecting small and medium sized vessels .Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) is positive in up to 40%–50% of cases [1]. This multisystem disease is typically characterized by 3 phases which include prodromal phase (with atopic disease, allergic rhinitis, and bronchial asthma), eosinophilic phase (peripheral blood eosinophilia or eosinophilic infiltration of multiple organs) and a vasculitic phase of which constitutional symptoms is a presage. Asthma and lung disease are the cardinal clinical features of EGPA and are present in more than 90% of the cases. Neurological involvement in EGPA is rare. Even in the presence of infrequent involvement of CNS in EGPA, it is usually seen in the later phase of the disease [1]. CNS is affected in 6% to 10% of patients with EGPA and it causes encephalopathy, ischemic infarcts or haemorrhages. (Murthy et al., 2013)[2] .This is a unique case of a patient with EGPA presenting with pan CNS and gut involvement at the diagnosis without lung or upper airway involvement.

Time Line

Jan 13,2019	Right knee join pain .Treated as “reactive arthritis”
July 13,2019	Admitted with acute abdominal pain. Diagnosed as appendicitis and undergone appendectomy.
July 14,2019	Detected o have hypertension.
July 23,2019	Admitted with bilateral, asymmetrical, spastic paraparesis and was diagnosed o have transverse myelitis .Stared on IV methyl prednisolone pulse therapy followed by prednisolone 1mg /kg.
Aug 05, 2019	Initial flaccid quadriparesis, later progressed o ascending spastic quadriplegia with a sensory level, bulbar involvement, Examination revealed a transient purpuric rash around ankle
Aug 06,2019	1.MRI Pan spine MRI brain showed ischemia of medulla oblongata, spinal cord and multiple infarctions of various ages in both cerebral hemispheres and the brain ,probably secondary vasculitis.
	2. Histology report of appendicular biopsy showed appendix with evidence of small vessel eosinophilic vasculitis and eosinophilic necrotic granuloma which was suggestive of EGPA
	3. ANA, C- ANCA, P- ANCA was sent. (Which came negative later.).Initial FBC on admission didn’t’ show hyper eosinophilia though noted in a FBC done previously.
Aug 06, 2019	Stared on IV methylprednisolone and cyclophosphamide pulse therapy with rheumatology opinion.
Aug 10,2019	Bulbar weakness resolved and upper limb power stared to improve.

Case Report Narrative

History A 31 year old Sri Lankan male who was recently discharged from hospital with the diagnosis of transverse myelitis, got admitted to the casualty ward with rapidly progressing flaccid quadriparesis and bulbar involvement over last 3 days.

His weakness of bilateral lower limbs started on the 21st of July 2019(which was the 10th postoperative day following an appendectomy) and it was progressive.

The weakness was more marked on left side and he tripped off while walking. He was conscious and afebrile. He had urinary retention, but there was no faecal incontinence. He denied having sensory symptoms back then. According to previous records he had bilateral spastic paraparesis (evident by power of left lower limb being 0, and right lower limb being 2 with bilateral up going plantar reflexes) without a sensory level, saddle anaesthesia or spinal tenderness. Anal sphincter tone was normal. Examination of his upper limbs, cranial nerves and cerebellum were clinically normal. He was investigated in a medical unit where the diagnosis of transverse myelitis was made based on his clinical presentation and MRI findings which demonstrated transverse myelitis involving 4^{th} to 7^{th} segment of spinal cord. He was referred to the neurology team who started him on IV methylprednisolone pulse therapy, physiotherapy and referred for rehabilitation after starting on oral prednisolone 1mg/kg. His muscle power improved significantly up to 4. Aetiology for transverse myelitis was not identified.

Unfortunately, following discharge the patient defaulted and presented again with worsening of neurology with weakness of all 4 limbs, dysarthria, dysphagia, sialorrhoea and weakness of neck muscles. Breathing was normal. He has lost his bladder and bowel control.

On inquiry he had an abdominal pain unrelated to meals for last 2 months and constitutional symptoms. He was anorexic and lost 3 kgs during last month. He also had a low grade intermittent fever during that period. He had a transient, non pruritic rash over bilateral legs. He didn't have active symptoms or signs of joint inflammation but had arthritis of his right knee joint following a sore throat a month ago and was diagnosed as having reactive arthritis. He denied having urinary symptoms, genitourinary discharges, gross haematuria or dark urine. He didn't have photosensitivity, facial rash suggestive of malar rash or alopecia. He denied having red eyes, genital or oral ulcers.

His bowel habits were normal. He didn’t have cough, rhinorrhoea or a headache suggesting sinusitis. There was no history of trauma, or features of increased intracranial pressure such as headache or vomiting.

According to the diagnosis card of his last hospital admission, he was admitted to hospital with severe central abdominal pain. USS showed inflamed appendix which was excised and sent for histology.

His past medical history revealed young hypertension (assessed and no secondary causes identified), for which he was on nifedipine 20mg bd for last 6 months.

He didn’t undergo any surgeries apart from the recent appendectomy. There were no neurological conditions in the family. He denied any allergies. He was a non-vegetarian, non-smoker and a social drinker.

Examination On admission he was conscious and rational with a GCS of 15/15 and was afebrile. He had a maculo papular rash on bilateral lower limbs. There was no lymphadenopathy or anaemia.

He had bilateral flaccid quadriplegia on admission with autonomic involvement. Power was 0 on both upper and lower limbs with bladder and bowel involvement. He also had bulbar palsy. His upper cranial nerves were normal. Cerebellar functions couldn't be assessed as patient had gross weakness. He had a sensory level at C5 and his pectoralis jerk was exaggerated indicating a motor level above C2. Patient was on a catheter without bladder

sensation. There were no organomegaly or ascites. His blood pressure was documented as 160/100 mmHg and pulse rate was 88bpm. Examination of the respiratory system was normal with vesicular breath sounds bilaterally. There were no added sounds or clinical evidence of a pleural effusion. After admission he developed bilateral spastic quadriplegia.

Differential diagnosis At the presentation, it was obvious that this patient was having a multisystem connective tissue disease with neurological involvement. The main differential diagnosis that were considered were systemic vasculitis due to small vessel vasculitis (eg: ANCA associated GPA, EGPA, MPO or non ANCA associated vasculitis such as IgA vasculitis or cryoglobulinemia), medium sized vessel vasculitis like PAN or secondary vasculitis due to Behcet's or SLE. Transverse myelitis due to any cause (Infections, tumours, vasculitis) was also a possibility. However primary CNS angiitis was less likely due to other systemic involvement.

Diagnostic assessment

MRI brain with C-spine was ordered (this was done with pan spine as marked expansion of the lesion was noted during assay when compared with the previous study) which revealed ischemia of medulla oblongata, spinal cord and multiple infarctions of various ages in both cerebral hemispheres and the brain, probably secondary vasculitis (Figure 1).

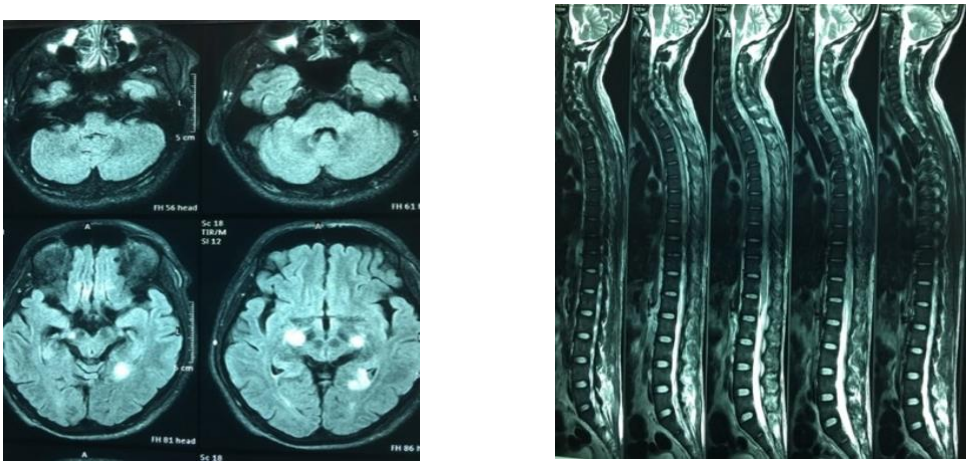

Figure 1:MRI Pan spine MRI brain showed ischemia of medulla oblongata ,spinal cord and multiple infarctions of various ages in both cerebral hemispheres and the brain ,probably secondary vasculitis.

Histology report of appendicular biopsy was traced which showed appendix with evidence of small vessel eosinophilic vasculitis and eosinophilic necrotic granuloma which was suggestive of EGPA (Figure 2).

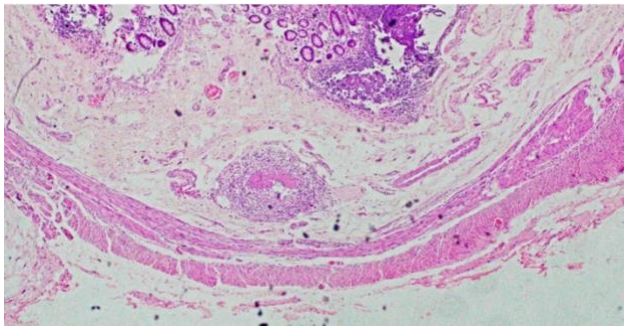

Figure 2: Appendicular biopsy showing eosinophilic, necrotic granuloma at 6 o'clock position with H and E staining.

Rest of the investigations are summarized in the table below.

Investigation	2019-07-24	2019-04-07
WBC (total white blood cells) 10^9/L	11.9	12.58
Lymphocytes	15%	12%
Neutrophils	76%	75%
Eosinophils	8%	11%
Haemoglobin	15.3	15
Platelet 10^9/L	493	357
CRP (mg/L)	26	
ESR in 1stHour (mm)	24	
Blood picture	normochromic, normocytic red cells, predominance of neutrophils with a left shift and thrombocytosis.	
ANA	Negative	
C ANCA	Negative	
P ANCA	Negative	
FBS(mg/dl)	104	
UFR	No active sediments or proteinuria	

Sodium	136mmol/L	
Potassium	4.3mmol/L	
Calcium	2.4 mmol/L	
Magnesium	0.7 mmol/L	
Creatinine phosphokinase	77 U/L	
Creatinine	57µmol/L	
BU	20mg/dL	
ALT	48U/L	
ALP	65IU/L	
Albumin	42 g/l	
Total protein	82g/L	
Bilirubin	4.3mg/dl	
HIV	Negative	
Hepatitis B and C	Negative	

Though the current FBC failed to demonstrate eosinophilia, a FBC done 6 months back for a routine medical check-up demonstrated marginal hyper eosinophilia (WBC -11670 U/L with an eosinophilia of 11%).

A lumbar puncture was done and CSF analysis showed, protein- 63.9mg/dL, glucose- 72mg/dL, polymorphs- Nil, lymphocytes - Nil, red cells - Nil, CSF oligo clonal bands- negative. Anti-aquaporin 4 receptor antibody was negative. Hepatitis B 's' antigen, and HIV is negative.

As the patient had flaccid quadriplegia at onset, a nerve conduction study was also done which excluded the possibility of Guillain-Barré syndrome.

Therapeutic intervention and follow-up

Liaising with the rheumatologist, the patient was told that his symptoms related to different organ systems were due to the unifying diagnosis of EGPA and he needs to be started on immunosuppressive treatment. Considering the evidence, age of the patient, severity of the disease, availability of medications at that point, and affordability, methylprednisolone with IV cyclophosphamide pulse therapy was initiated. Prednisolone and azathioprine used for maintenance, together with rehabilitation.

Reversal of the bulbar weakness was the earliest feature of his recovery followed by improvement of the upper limb power to 4+ over weeks. The patient achieved full recovery of the upper limb functions over next few months and returned to work on wheelchair. Lower limb weakness is not fully recovered, but he is improving slowly. His follow-up was arranged at the rheumatology clinic. Apart from one episode of uncomplicated acute gastroenteritis, he didn't have any complications related to immunosuppressive treatment.

Discussion

EGPA is the rarest of ANCA positive small vessel vasculitis and is usually evolve over decades. Considering the pathology, the most distinctive feature of EGPA is deposition of eosinophils rich granulomas in tissues. Traditionally, EGPA follows a course of three phases which starts with an initial prodromal phase marked by asthma, rhinitis, sinusitis and/or nasal polyposis or eosinophilic gastroenteritis. The next phase follows later on when pulmonary

infiltrates and peripheral eosinophilia predominate. The latest manifestation of the disease is the third phase with vasculitic manifestations (eg: polyneuropathies, skin lesions, gastrointestinal ischemia, and glomerulonephritis.) [1]

Due to its prolonged course and erratic presentation of symptoms which overlap at different times, EGPA is a challenging diagnosis to make if one strictly adheres to the triphasic pattern of the disease especially in a case like this when the patient presents in the latter phase without the typical history of atopy. Unless identified and treated swiftly, the ramifications would be devastating leading to high mortality and morbidity [3].

Central nervous system angiitis, gastrointestinal manifestations and cardiac manifestations are phenomenal clinical manifestations of EGPA in contrary to the usual asthma, rhinitis and sinus disease, polyneuropathy and skin lesions [3].

At the presentation, seeing a young patient with progressive spastic quadriplegia with bladder and autonomic involvement and a sensory level, a maculo papular rash , background of arthritis and hypertension, gastrointestinal involvement, several differential diagnoses were considered and the most likely cause was systemic vasculitis due to small vessel vasculitis (eg:ANCA associated GPA,EGPA,MPO or non ANCA associated vasculitis such as IgA vasculitis or cryoglobulinemia), medium sized vessel vasculitis like PAN or secondary vasculitis due to Bechet, SLE. Transverse myelitis due to any cause (Infections, tumours, vasculitis) was also a possibility. However primary CNS angiitis was less likely due to other systemic involvement.

Central nervous system manifestations in EGPA can be divided in to 4 main categories. These include cerebral ischemic lesions, intracerebral haemorrhages, cranial nerve palsies and loss of visual acuity. Ischemic lesions were the commonest manifestation, representing more than 50% of cases [4].This was the case in our patient as well. Based on clinical and radiological findings, CNS involvement due to EGPA appears to be similar to those of primary CNS angiitis [4], with motor and sensory deficit. In our patient, skin or

the nerve biopsy was differed pending the histology report of appendicular biopsy. However, the available literature state that nerve biopsy is usually unnecessary in patients with confirmed EGPA who present with limb pain, paraesthesia, and sensory and/or motor loss [3].

Gastrointestinal symptoms are common (3145% of cases) in EGPA and range from mild abdominal pain, nausea and vomiting to intestinal necrosis due to mesenteric ischemia. Even though GI symptoms are common, lesions are seen in only 20% of the cases.

Though histological diagnosis is preferred, it is not feasible always. Histopathologically EGPA is characterised by small necrotizing granulomas, and vasculitis of small and medium vessels. The granulomas consist of a central eosinophilic core surrounded radially by macrophages and epithelioid giant cells, which were seen in the appendicular biopsy of the above patient [5].

Disease severity in EGPA is quantified using Five factor score (FFS) devised by the French Vasculitis Study Group. Not only it quantifies disease severity but also is helpful in establishing initial management and treatment [6]. The 5-year survival probability falls from 90% with an FFS of 0 to 65% with an FFS of >2.

In mild disease, glucocorticoid alone is the treatment [3]. An induction regimen adding another immunosuppressant (usually cyclophosphamide) to glucocorticoids is used in treating severe disease. In mild to moderate disease methotrexate or azathioprine is used instead of cyclophosphamide. Maintenance therapy (with azathioprine or methotrexate) is recommended for patients with life- and/or organ-threatening disease manifestations [7]. Rituximab is the treatment for selected ANCA positive patients with renal involvement or refractory disease [7]. Plasma exchange is the treatment for selected patients with ANCA and rapidly progressive glomerulonephritis or pulmonary-renal syndrome. Intravenous immunoglobulin is a second-line therapy for patients on glucocorticoids (and/or other immunosuppressant's) with EGPA flares refractory to other treatments or during pregnancy.

Interferon-alpha is a second- or third line drug for selected patients.
Leukotriene receptor antagonists can be prescribed, if needed, for EGPA patients [7]. A promising future therapy is mepolizumab [8].
Overall, CNS involvement occurring in the setting of EGPA is associated with a poor organ and/or life-threatening prognosis. In contrast, outcome of cranial nerve palsies seemed to be better with 25% of long-term sequale.
Although approximately 90% of patients with EGPA develop asthma in their adulthood or may present with worsening of long standing asthma our patient never had a history of respiratory symptoms [9]. Reason for our patient not having pulmonary lesions identify would be that the CXRs and HRCT scan were done when the patient was asymptomatic and theses lesions are also transient. He was also on steroid therapy prior to the current admission which may be contributory to disappearance of pulmonary lesions if there were any.
History and radiological assessment ruled out sinus pathology.
Skin lesions are very common in EGPA. The most frequently seen is palpable purpura which was seen in the above patient too. Other lesions include subcutaneous nodules, ulcers, urticaria and digital ischemia. However, we didn't go ahead with a skin biopsy as it may not yield any additional information.
Eosinophilia was not recorded on this admission as expected since patient was on steroid treatment and presented in the vasculitic phase rather than in the eosinophilic phase. But, he had marginally high eosinophilia on a previous blood report done.
The antineutrophil cytoplasmic antibodies (ANCA) which occurs in only 30% to 40% of patients, was not seen in the above patient and it is not a must for the diagnosis.

Conclusion

EGPA may not always follow the typical triphasic pattern of the disease. Unlike in classical EGPA, the atypical presentations may lead to delay in the diagnosis if the whole picture is not taken into consideration.

CNS vasculitis due to EGPA is rare. Deposition of eosinophilic granuloma in gut is rare in EGPA though the gastrointestinal symptoms are common. Hyper eosinophilia may not always seen at presentation if patient presented in the vasculitic phase. Prompt identification of the disease with atypical presentations, prognostication and early use of cytotoxic therapy when indicated would improve the outcome.

Informed written consent :obtained

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3. Dr. Anoma Perera,Consultant Pathologist, TH Karapitiya
4. Dr.Upul de Silva, Consultant Physician, TH Karapitiya

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The story of a landmine: A patient with melioidosis presenting with multiple abscesses

Case number : 02

Name of the Consultant : Dr.Upul de Silva

Name of the PGIM trainee : Dr.P.W.G. Chamika

Name of the patient :Mr.K.G.Bandusiri

Age :57 years

Ward number :19

Name of the Hospital :Teaching Hospital Karapitiya

BHT :111963

Date of admission :02.09.2018

Date of discharge :14.10.2018

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Supervising Consultant

The story of a landmine: A patient with melioidosis presenting with multiple abscesses

Abstract

Introduction Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei*, a saprophyte found in soil or contaminated water. It causes a clinical spectrum of infection that may range from an acute, fulminant sepsis to chronic, localized infection resulting in abscess formation. It is typically seen in tropical belt.

Case presentation A 57 years old patient with diabetes with a background history of heavy alcohol abuse, involved in tourism and floriculture presented with a high grade intermittent fever and constitutional symptoms with dark urine for 3 weeks. He gave a history of incision and drainage of a thoracic wall abscess 3 months back. He was febrile, pale and icteric with normal systemic examination. He was diagnosed to have melioidosis according to a positive blood culture. USS showed a focal lesion in segment V and VII of his liver and it was suggestive of a hepatoma. However, the alpha fetoprotein was 0.996, and it was negative. A triple phase CT scan abdomen was done which revealed, a 7.5cm X 5.4cm X 5.4cm size resolving liver abscesses in segment VI and VII with multiple micro abscesses in spleen and multiple renal abscesses.In the intensive phase, IV meropenem was continued for 6 weeks. Oral cotrimoxazole, doxycycline, and folic acid were administered according to his body weight for 3 weeks in the eradication phase. After starting treatment in the intensive phase, patient became afebrile, was stable, had improved markers of inflammation and repeated USS showed resolving liver abscess, splenic abscess and renal abscess. He was discharged after 6 weeks of intravenous antibiotics .He was followed up during the eradication phase which was continued for another 3 months as patient had multiple abscesses.

Conclusion Melioidosis is a fairly uncommon cause for pyogenic liver abscess. Though mortality is high as 50% in patients with melioidosis not received appropriate antibiotics, it can be brought down significantly with administration of appropriate antibiotics. Surgical interventions may not be feasible in cases of multiple abscesses. Close monitoring, follow-up and patient education helps in detection of relapses early.

Key words: case report, Melioidosis, multiple liver abscesses, renal abscess, splenic abscesses, pyrexia of unknown origin

Introduction

Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei*, a saprophyte found in soil or contaminated water [1]. It is a facultative, intracellular, Gram-negative and oxidase positive bacillus which causes a clinical spectrum of infection that may range from an acute, fulminant sepsis to chronic, localized infection resulting in abscess formation [2]. It is typically seen in tropical countries such as South-East Asia, South Asia, Northern Australia & China. Sri Lanka lies in the melioidosis endemic belt between 5°N and 10°N surrounded by countries known to be endemic to melioidosis [3], but it was not identified as an endemic disease in Sri Lanka until recently [4] despite the fact that it's economy still based on agriculture mainly. The infection is acquired by inoculation or inhalation of contaminated soil and water.

Males were predominantly affected (71.6%) and the age range was wide (2–92 years) reflecting a ubiquity of exposure. Out of all cases diagnosed the majority (80%) lived in rural areas but all provinces were affected. Case load increased during the two monsoonal periods (67%). When considered, there was representation of every population group including farmers, housewives, students, professionals, businessmen and etc. People with an underlying predisposition such as diabetes mellitus, renal disease, liver disease or alcoholism are more prone to get severe disease but out of all diabetes was the predominant risk factor (65.2%). [1]

Time Line

Oct 11, 2016	Diagnosed diabetes
May 04, 2018	Drainage of a thoracic wall abscess
Aug 09,2018	Onset of a high grade intermittent fever with constitutional symptoms and passage of dark urine. This lasted for 3 weeks prior to hospital admission.
Sep 02,2018	Admitted to hospital. After cultures a broad spectrum antibiotic started. Initial blood culture was negative
Sep 03,2018	USS showed a focal lesion in segment V and VII of his liver and it was suggestive of a hepatoma
Sep 05,2018	Blood culture positive for *B.pseudomallei*
	A triple phase CT scan abdomen was done which revealed, a 7.5cm X 5.4cmX 5.4 cm size resolving liver abscesses in segment VI and VII with multiple micro abscesses in spleen and multiple renal abscesses.
	IV meropenem continued for 6 weeks with marked response of clinical parameters and inflammatory markers
Sep 17, 2018	Repeat USS- resolving liver and splenic abscesses
Oct 13, 2018	Eradication phase stared and patient was discharged. Followed up in the clinic with no evidence of relapse.

Case Report Narrative

History

A 57 years old businessman diagnosed with type 2 diabetes for 1 ½ years without micro or macro vascular complications on oral hypoglycaemic agents with a recent poor control despite good adherence with the treatment plan, presented with fever for 3 weeks. He had a high grade intermittent fever associated with chills and rigors without a diurnal variation. It responded poorly to antipyretics. He had anorexia and loss of weight. He had associated arthralgia and myalgia. He noticed passing "dark" urine without other urinary symptoms. He denied having a cough. His bowel habits were normal.
There was no history of transfusion. He has undergone an incision and drainage of a left sided thoracic wall abscess 3 months ago. Unfortunately, the pus was not sent for culture back then. He was involved in tourism in Sri Lanka. He denied sexual promiscuity or drug abuse. He had a special interest in floriculture and consumed 10 units of alcohol daily for 30 years.

Examination

On examination the patient was pale, icteric, febrile and ill. There was no hepatosplenomegaly or lymphadenopathy. There was no nuchal rigidity. Apart from icterus and pallor there were no peripheral stigmata of CLCD or infective endocarditis. His lungs were clear, and there were no murmurs. The temperature chart showed high spiking intermittent fever varying from (100-104^{o}F). He was hemodynamically stable with a blood pressure of 110/70mmHg.

Diagnostic assessment

His initial FBC showed a WBC of 7.04×103/L, with a neutrophil count of 5.11×103/L, lymphocytes of 1.38×103/L, haemoglobin of 12.7 g/dL, HCT of 35.3%, platelets 286,000/UL. However, he developed pancytopenia on the 13thday of his hospital admission and how his FBC changed overtime is demonstrated under diagnostics below. Initial blood picture showed bicytopenia probably due to chronic infection or inflammation. His ESR was 128 mm /hour, and CRP was 246 mg/dL. His coagulation profile was normal. In urine analysis, he had microscopic haematuria and urine bile salt was positive. His urine culture was sterile. His initial blood culture didn't grow any organism. A chest radiograph was done and it was reported as normal by the radiologist. USS showed a focal lesion in segment V and VII of his liver and it was suggestive of a hepatoma. However, the alpha fetoprotein was 0.996 , and it was negative. A triple phase CT scan abdomen was done which revealed, a 7.5cm X 5.4cmX 5.4 cm size resolving liver abscesses in segment VI and VII with multiple micro abscesses in spleen and multiple renal abscesses (Figure 3).

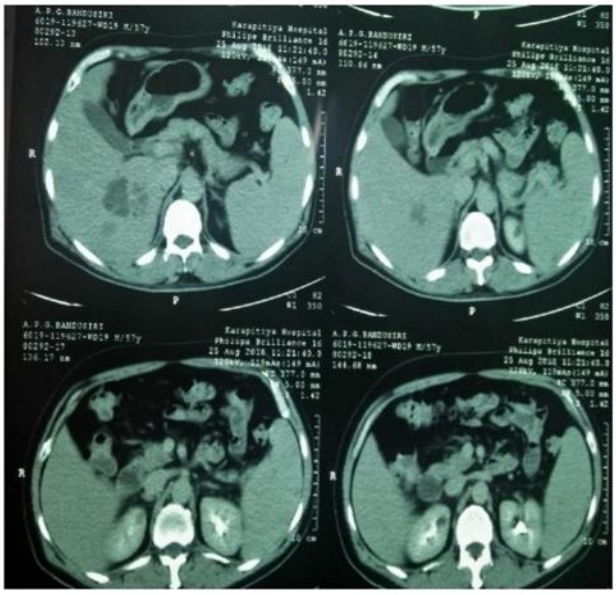

Figure 3: Triple phase CT abdomen CT features are in favour of 7.5x5.4x5.4cm size resolving liver abscess in segment VI and vii with multiple splenic micro abscesses and right side renal abscess. Mild splenomegaly.

As the patient was ill, multiple blood cultures were repeated with the fever spikes and later on it was positive for Burkholderia pseudomallei and patient was diagnosed as having melioidosis. Melioidosis antibody titre was negative, 1:60. His FBS was 346mg/dL on admission. His 2D Echocardiogram didn't show evidence of infective endocarditis and it was normal. However, a transoesophageal echocardiogram was not done. Retroviral screening, Hepatitis B's' antigen and Hepatitis C antibody were negative. Mantoux test was negative. Brucella antigens were negative.

Diagnostics

DATE	TYPE	VALUE	UNIT
2018-09-02	Hb (hemoglobin) Hct (hematocrit)	12.7 35.3	g/dl %
	WBC (total white blood cells) Lymphocytes Neutrophils	7.04 1.38 5.11	$\times 10^9$ cells/L
	Platelet count	286	x 10^9 cells/L
	CRP (C-reactive protein) ESR	246 128	mg/L mm/1^{st} hr
	Blood culture	*B.pseudomallei*	
2018-09-02	AST (aspartate aminotransferase)	168	U/L
	ALT (alanine aminotransferase)	120	U/L
	ALP (alkaline phosphatase)	162	U/L
	GGT (gamma-glutamlytransferase)	321	U/L

	Albumin	33	g/L
	Sodium Potassium	131 4.2	mmol/L
	FBS	346	mg/dl
	Creatinine	136	μmol/L
2018-09-06	Alfa fetoprotein	0.996	ng/ml

Therapeutic interventions

Patient was weighing 63.5kg and depending on his body weight treatment stated in 2 phases. In the intensive phase, patient was given IV meropenem 1g 8hourly and oral cotrimoxazole 1920mg bd, according to his body weight for 6 weeks. In eradication phase he was started on oral cotrimoxazole 1920mg bd, oral doxycycline 100mg bd, and oral folic acid 5mg/d. He was discharged after 6 weeks of intravenous antibiotics and was followed up as an outpatient in eradication phase where treatment was continued for another 3 months as patient had multiple abscesses.

After starting treatment in the intensive phase, patient became afebrile, was stable, had improved markers of inflammation and repeated USS showed resolving liver abscess, splenic abscess and renal abscess.

Follow up

During and the eradication phase he was followed up in the clinic for a period more than a year and he recovered completely.

Discussion

Pyogenic liver abscess is the consequence of bacterial infection of the liver parenchyma, resulting in infiltration by inflammatory cells and formation of

pus. In 1988, a study revealed that CT scan is superior to USS in detection of pyogenic liver abscess [5]. The sensitivity of USS in detection of a liver abscess depends on the size, site of the abscess and underlying comorbidities [6]. The commonest cause for a pyogenic liver abscess is ascending infection from biliary tract, followed by haematogenous spread [7]. Out of all, E. coli is the most often cultured bacteria, accounting for about 33% of the cases followed by streptococcal group [8]. Melioidosis is a fairly uncommon cause for pyogenic liver abscess.

In this case, with the history of recent poor control of diabetes and drainage of a thoracic wall abscess, most likely differential diagnosis considered were either a deep-seated abscess as a result of a recurrent systemic infection such as a pyogenic infection, melioidosis, or typhus, or renal carcinoma with hepatic metastases or a hepatic carcinoma.

A liver abscess is difficult to be distinguished from hepatic tumour necrosis clinically, serologically or radiologically [9].The radiographic appearances of hepatic abscesses range from well circumscribed cystic lesion with enhancing rim to heterogeneously enhancing mass-like lesion, which is sometimes indistinguishable from hepatic neoplasm[10].Our patient showed the features like acute onset illness with the presence of fever, and elevated inflammatory markers supporting the presence of liver abscess clinically. On the other hand, apart from the history of chronic alcohol abuse, he didn't have other risk factors for development of HCC. He was sero-negative for hepatitis B and C, had no imaging findings consistent with cirrhosis. But he never had elevated leukocyte count which was expected in liver abscess. Instead he had pancytopenia which is an observed finding in melioidosis due to bone marrow suppression. Although clinically the diagnosis seemed to be a liver abscess, ultrasound scan was more suggestive of a hepatoma initially with a sterile blood culture. This leads to further assessment by four phase CT abdomen and Alpha fetoprotein which were negative. However, in 40% of all hepatoma, Alpha fetoprotein is negative and these are referred as non-secretory hepatoma

[11]. Several studies were done comparing diagnostic accuracy of USS as a screening tool for early detection of HCC[11].The sensitivity increased up to 79%, when combined with AFP assessment. One systematic review concluded that the specificity of USS was 97% (95%CI: 95%-98%) and sensitivity was 60% (95%CI: 44%-76%) compared with pathologic assessment of resected liver as a standard reference [11].The same systematic review estimated that when using CT, the specificity was 93% (95%CI: 89%-96%) and the sensitivity was 68% (95%CI: 55%-80%) compared with pathologic tissue examination of resected liver as the reference standard. MRI is superior to both US and CT in differentiating the nature of regenerative nodules from HCC nodules in the patient with cirrhosis [11]. These support the diagnosis of liver abscess over HCC in this patient. Visceral organ abscesses appear on ultrasound as multiple and small hypo echoic lesions, target lesions and multi loculated lesions. Melioidosis gives rise to characteristic CT appearance with the “necklace sign” or the ”honeycomb sign” with multi-loculated lesions [6] .Simultaneous liver and splenic abscesses are more likely to be associated with melioidosis. Definitive diagnosis is made by culture and isolation of the organism from blood or infected organ.

Melioidosis has a broad spectrum of clinical disease varying from asymptomatic infections and localized skin abscess without systemic illness to fulminant diseases with abscesses involving lungs and other internal organs. The latter picture is usually seen when the host is immuno-compromised. Melioidosis is divided into subclinical, acute and chronic disease. Acute cases are those where symptoms were present for <2 months. The lung is the most commonly affected organ [2]. Out of intra-abdominal organs infected by melioidosis, ,spleen is the most commonly affected followed by the liver and kidney[12]. The treatment of choice is intravenous ceftazidime (or) meropenem 6-8 hourly followed by 3-6 months of co-trimoxazole (or) doxycycline therapy. There is Grade 2 C evidence to suggest addition of cotrimoxazole to ceftazidime or a carbapenem during initial intensive therapy may be beneficial

as it has an excellent tissue penetration when the patient has non pulmonary disease as in this case. Our patient was given oral cotrimoxazole plus doxycycline in the eradication phase in contrary to the use of doxycycline alone in the eradication phase according to the local guideline. However, a randomized, multicentre, double-blind trial done in Thailand suggests that in this practice, cotrimoxazole plays the critical component of this combination regimen [16].

Minimal criteria for switch from intensive to eradication phase included being afebrile more than 48 hours, having negative blood cultures when repeated 7 days after treatment and when patient can take orally. The desirable criteria would be having a good clinical and CRP response.

Though mortality is high as 50% in patients not received appropriate antibiotics [13] , it can be brought down significantly with correct diagnosis at correct time and administration of appropriate antibiotics as in our patient. In addition to chronic forms, melioidosis can be reactive as well. Thus, treatment with oral antibiotics in the eradication phase is of utmost importance. The duration of the intensive phase and eradication phase vary according to the site involved and presentation. According to Dawin melioidosis guideline, for deep seated multiple abscesses, the intensive phase extends for 4 to 6 weeks, while eradication phase treatment should be continued for 3 months to expect low relapse rates with good evidence for efficacy [14] , but a small number of patients may require a longer period of Phase 2 eradication treatment. These are patients with extensive underlying comorbidity where complete eradication is unrealistic, particularly when the disease is multifocal and unresponsive to antimicrobial agents [14]. Surgical intervention, drainage of the abscess, either through percutaneous approach or laparoscopically, or as an open procedure, has shown good outcomes in cases of single liver abscess [15]. But our patient had multiple abscesses including micro abscesses at multiple sites making surgical drainage an unrealistic

option. He also responded well to antibiotics, with complete resolution of abscesses in follow-up scans.

Conclusion

Melioidosis is a fairly uncommon cause for pyogenic liver abscess. CT scan is superior to USS in detection of liver abscess. Sensitivity of USS in detection of a liver abscess depends on the size, site of the abscess and underlying comorbidities.

Previous studies demonstrated that a liver abscess is difficult to be distinguished from hepatic tumour necrosis clinically, serologically or radiologically.

Acute onset illness with the presence of fever, and elevated inflammatory markers and a high neutrophil leucocytosis support the presence of liver abscess over hepatocellular carcinoma clinically. Definitive diagnosis of melioidosis is made by isolation of the pathogen from blood or infected organ / tissue culture.

Though mortality is high as 50% in patients not received appropriate antibiotics, it can be brought down significantly with correct diagnosis at correct time and administration of appropriate antibiotics as in our patient.

In addition to chronic forms, melioidosis can be reactive as well. Thus, treatment with oral antibiotics in the eradication phase is of utmost importance following treatment with IV antibiotics in intensive phase. The duration of the intensive phase and eradication phase vary according to the site involved and presentation. Surgical interventions may not be feasible in cases of multiple abscesses. Close monitoring, follow-up and patient education help in early detection of relapses.

Informed written consent: Obtained

Acknowledgements

1. Dr.Bhagya Piyasiri, Consultant Microbiologist, TH Karapitiya
2. Dr.Upul de Silva, , Consultant Physician, TH Karapitiya

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A patient with dengue haemorrhagic fever complicated with neuroleptic malignant syndrome following administration of metoclopramide: A diagnostic dilemma

Case number : 03

Name of the Consultant : Dr.Upul de Silva

Name of the PGIM trainee : Dr.P.W.G. Chamika

Name of the patient :Mr.Gamith Chanuka

Age :17 years

Ward number :19

Name of the Hospital :Teaching Hospital Karapitiya

BHT : 135333

Date of admission :08.10.2019

Date of discharge :21.10.2019

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Supervising Consultant

A patient with dengue haemorrhagic fever complicated with neuroleptic malignant syndrome following administration of metoclopramide: A diagnostic dilemma

Abstract

Introduction Neuroleptic malignant syndrome is a severe, life threatening, idiosyncratic reaction due to certain neuroleptic agents, antiemetics and withdrawal of anti- Parkinsonism characterized by rigidity, dyskinesia, altered sensorium, and dysautonomia. As it results in high mortality if not treated promptly it is considered a neurological emergency.

Case presentation A 17 year old patient presented with fever for 3 days associated with arthralgia, myalgia, vomiting and loose stools. He was diagnosed to have dengue haemorrhagic fever and recovered from critical phase on the 7th day of the illness. Even after entering the recovery phase, the patient had persistent fever, with altered sensorium, dystonia autonomic instability and generalized rigidity with hypo-reflexia. Depending on the history of administration of oral and then IV metoclopramide to control vomiting in a patient with dengue haemorrhagic fever, along with biochemical markers of elevated CPK to more than 60 times confirmed the diagnosis of neuroleptic malignant syndrome due to metoclopramide. He was started on treatment with IV dantrolene, followed by oral bromocriptine, which improved his symptoms and outcome. This is a unique case report of a dengue haemorrhagic fever complicated with neurological sequale following neuroleptic malignant syndrome caused by use of metoclopramide.

Conclusion NMS is a diagnosis by exclusion paying detailed attention to possible exposure, symptoms, a careful neurological examination, and a panel of laboratory investigations. When it develops on top of another febrile illness, the diagnosis is further difficult. When recognized and treated early, majority of patients recover completely within 2 weeks. If not patients may take longer periods for recovery with residual neurological impairment. Sometimes death may occur as a result of renal failure, arrhythmia, DIC or cardiopulmonary complications.

Key words: case report, neuroleptic malignant syndrome, Metoclopramide, Dengue haemorrhagic fever

Introduction

Neuroleptic malignant syndrome (NMS) is a severe, life threatening, idiosyncratic reaction due to certain neuroleptic agents, antiemetics and withdrawal of anti- Parkinsonism medications. It is a neurological emergency which manifests as generalized rigidity, especially lead- pipe rigidity, dyskinesia, altered sensorium, and dysautonomia.

It is described in all age groups from 0.9 to 78 years [1] but most patients are young adults though age is not a risk factor [2]. It was more prevalent in males.

Mortality due to neuroleptic malignant syndrome has reduced over the years due to increased recognition and improved treatment. However when it occur, mortality is directly related to dysautonomic manifestations of the disease or systemic complications.

The high-potency first-generation antipsychotic agents are well documented to cause neuroleptic malignant syndrome. But, even the low potency antipsychotic agents as chlorpromazine, atypical antipsychotics (eg, clozapine, risperidone, olanzapine) and antiemetics (eg, metoclopramide, promethazine) [3] can cause neuroleptic malignant syndrome. Symptoms usually develop during the first two weeks of therapy with the causative agent. NMS can occur after a single dose or even after treatment with the same agent in same dose for several years. Though not dose-dependent, higher doses, recent or rapid dose escalation, switching between neuroleptic agents and parenteral administration are known risk factors [2]. Concomitant use of lithium, use of depot formulations or higher potency agents, comorbid neurological conditions, substance abuse and acute trauma, surgery, and infection escalate the risk of NMS markedly[2].Dehydration, was observed in a majority of patients. However it is unclear whether it is a risk factor for, or an early complication of, NMS [2].

Time line

2019-10-05	Fever, retro-orbital pain, arthralgia, myalgia, and vomiting
2019-10-06	Treated by General practitioner with paracetamol, metoclopramide and ciprofloxacin
2019-10-07	Admitted to hospital and diagnosed as Dengue.
2019-10-09	Start of Critical phase. Complicated with symptomatic hypocalcaemia at the end of 24 hours which was corrected.
2019-10-11	End of critical phase
2019-10-12	Diagnosed neuroleptic malignant syndrome due to history of metoclopramide, hyperthermia, confusion, with rigidity and diminished reflexes. His CPK was high. Cultures were sent to exclude a secondary infection. Immediate withdrawal of metoclopramide. Treated with IV Dantrolene with marked response.
2019-10-14	Dantrolene was replaced with bromocriptine.

Case Report Narrative

History

A 17 y old patient, presented with fever for 3 days associated with nausea, vomiting, loose stools and severe arthralgia. Fever was preceded by a frontal headache associated with retro-orbital pain. Flushing of the skin was noted. He had profuse vomiting, loose stools and complained of mild postural dizziness on admission. According to the patient he was passing and normal amount of urine. He denied having myalgia, cough, urinary symptoms, or bleeding manifestations. He denied having a history suggestive of a possible exposure to leptospirosis. He was residing in an urban area. He was seen by the local GP on day 2 of fever, and was started on oral paracetamol, metoclopramide, ciprofloxacin and omeprazole. He was apparently well until the onset of fever. He did not have any allergies in the past.

Examination On examination, the patient was flushed, febrile with a temperature of 100-4˚ F on admission, and mildly dehydrated. He didn't have lymphadenopathy, rashes or eschars. He was not pale or icteric. He was hemodynamically stable on admission with a pulse rate of 80 bpm, and a blood pressure of 100/70mmHg without a postural drop. Bilateral lung fields were clear without evidence of consolidation or pleural effusions. His abdomen was not distended and non-tender without hepatosplenomegaly or ascites. The bowel sounds were normal.

Differential diagnosis Considering the epidemiology and clinical presentation, dengue fever/ dengue haemorrhagic fever was the first differential diagnosis as the patient presented in a monsoon season with fever from an urban area where prevalence of dengue was high. Other differential diagnoses were acute gastroenteritis due to viral or bacterial origin, leptospirosis, typhoid or typhus .

Investigations on admission Initial FBC showed leucopoenia and thrombocytopenia with a WBC of 6030 /UL, Lymphocyte of 3880/UL with a neutrophil count of 1960/UL. Haemoglobin was 12g/dI with a haematocrit of 36%, and platelet count of 110,000/UL. CRP was 20 mg /L. ESR was 15 mm/, 1st hour. Dengue NS1 was positive. Bedside USS ,done on admission on 3rd day of the illness was negative. His ALT was 88/UL ALT 105 /UL on admission.

On the 5th day of the illness, patient entered the critical phase. A right sided pleural effussion was detected on bed side USS. Haematocrit increased to 42%. The lowest platelet count was 25,000/UL. AST increased up to 667/ UL. The lowest albumin level noted during critical phase was 25mg/dL.

Management of DHF

The patient was managed according to current Sri Lankan guideline of managing DHF.

Temperature chart marked persistently elevated body temperature above the baseline throughout the critical phase. On Day 6 of fever he had tetany due to hypocalcaemia of 7.6mg/ dl (8.610.3) which was improved with IV calcium gluconate (10%) replacement.

Towards the end of the critical phase, his PCV, WBCs, platelets and other parameters were improving and the patient entered the recovery phase on Day 8 of fever. His WBC count 18700U/L with neutrophil predominance and CRP was elevated to 100mm/1st hour. He had evidence of left forearm cannula site infection. He was started on oral flucloxacillin after a blood culture. But the patient remained febrile, and flushed. He became agitated and confused and was reluctant to converse which was not usual of him. He had a tremor, dystonia and sialorrhoea with swallowing difficulty. He had generalized rigidity & lead pipe rigidity could be demonstrated on upper and lower limb examination. He complained of a dysphagia, dysarthria and myalgia. The patient had a profuse diaphoresis and remained tachypneic with a pulse rate of

104- 120bpm even in the recovery phase. He had deep flushing and peeling off of the skin in his faces and groin. The examination revealed a febrile, flushed drowsy patient of GCS 14/15. He had desquamation of skin on face & groin. Left forearm thrombophlebitis was noted. The proper neurological examination has revealed a sustained asymmetrical tremor involving all 4 limbs, more marked on the right. He had neck stiffness and generalized rigidity with increased tone in both his upper and lower limbs. The power of bilateral upper and lower limbs was 4+. Reflexes were diminished. There were no focal neurological signs identified. Even after settling of the cannula site infection, he had persistent high spiking fever with improving WBC & CRP. At this point several differential diagnoses were considered to explain the worsening of clinical picture and they include, neuroleptic malignant syndrome (NMS), heat stroke, central nervous system (CNS) infections, toxic encephalopathies, agitated delirium, status epilepticus, and more benign drug induced extrapyramidal symptoms.

Diagnostics

To exclude the possibility of meningoencephalitis a lumbar puncture was done after exclusion of increased intracranial pressure clinically and radiologically (by a normal NCCT brain), and when the platelet count was rising and above 85000/cumm which was having a normal full report.

Dengue IgM & Ig G antibodies were positive in CSF, but Dengue PCR in CSF was negative.

EBV, CMV, HSV 1 and 2, VZV antibodies in CSF were negative. EEG showed moderate encephalopathy. His serum creatinine was 0.7 mg/dl with negative urine myoglobin.

Excluding most of the infectious causes, possibility of the patient having a hyperthermia rather than ‘fever’ was considered high up the in differential diagnosis which could explain almost all of his symptoms.

A serum CPK value of 18,680 U/L confirmed the diagnosis of neuroleptic malignant syndrome. His serum creatinine remained normal throughout. A summary of the diagnostics is given below.

DATE	TYPE	VALUE	UNIT
10/8/2019	WBC (total white blood cells)	6034	UL
10/8/2019	Neutrophils	1960	UL
10/8/2019	Lymphocytes	3880	UL
10/8/2019	Haemoglobin	12	g/dl
10/8/2019	Haematocrit	36	%
10/8/2019	Platelet	110,000	UL
10/8/2019	AST	105	IU/L
10/8/2019	ALT	88	IU/L

10/8/2019	ESR	19	mm/1st hour
10/8/2019	CRP	20	mg/L
10/15/2019	CPK	18800	IU/L
10/13/2019	Calcium	7.6	mg/dl
10/15/2019	Creatinine	0.7	mg/dl

Management of NMS

Metoclopramide was stopped immediately. Patient was started on cooling methods such as ice packs, cool normal saline infusion, and hydrated with oral & IV fluids.

He was started on IV dantrolene (2.5mg/kg) 40mg 6 hourly, and continued until 72 hours with good response indicated by improving neurology, absence of fever and reduction in CPK. Once patient was stabilized dantrolene was replaced by oral bromocriptine 5 mg bd.

On day 16 of infection (day 13 of hospital stay), he was discharged from hospital with full recovery. His FBC returned to normal and CRP was 2mg /L. His CPK dropped to 300 U/L which was in the normal range. He returned school the next week and on follow up there were no neurological sequale.

Discussion

Neuroleptic malignant syndrome diagnostic criteria was published by an international multispecialty consensus group for NMS in 2011 based on

clinical and laboratory criteria which include exposure to dopamine antagonist, or dopamine agonist withdrawal, within past 72 hours, hyperthermia (>100.4°F or >38.0°C on at least 2 occasions,), rigidity, mental status alteration, Creatine kinase elevation (at least 4 times the upper limit of normal), sympathetic nervous system lability, defined as at least 2 of the following, blood pressure elevation (systolic or diastolic ≥25 percent above baseline), blood pressure fluctuation (≥20 mmHg diastolic change or ≥25 mmHg systolic change within 24 hours), diaphoresis, urinary incontinence, and hyper metabolism, with negative work-up for infectious, toxic, metabolic, or neurologic causes[6]. In instances CPK can be normal if rigidity is not markedly developed . Leucocytosis is also known to be associated with neuroleptic malignant syndrome (NMS) [5].

Important differential diagnosis that must be considered in any patient with possible NMS include meningitis, encephalitis, systemic infections, heat stroke, and other drug-induced dysautonomia. Of course, in our patient he was already febrile due to DHF at the time he developed NMS which made the diagnosis difficult. Identifying the persistent fever as a result of a different pathology rather than the prolong fever due to disease 'itself' or a superadded infection was the turning point of the management. . But when analysing the case retrospectively, apart from administration of oral followed by parenteral use of metoclopramide, he had other risk factors which made him more vulnerable to get NMS such as infection and dehydration.

However, the other main consideration was whether this was a dengue encephalitis though it was a rare manifestation. The criteria for dengue encephalitis was defined by fever, acute signs of cerebral involvement, presence of anti-dengue IgM antibodies or dengue genomic material in serum and/or CSF and exclusion of other viral encephalitis and encephalopathy[7]. This patient had positive IgM in CSF, with negative Dengue NS 1antigen RT-PCR in CSF. Detection of immunoglobulin in CSF is possibly due to increased permeability of the blood-brain barrier to proteins with acute

infection or local release antibodies into the CSF by lymphocytes due to direct CNS invasion by virus. When combined with RT-PCR and IgM specificity of dengue neurological involvement increases up to 92% in the absence of other causes. But as there was another explanation for the neurological deterioration, and RT PCR became negative, the positivity of IgM thought to be due to disturbance to blood brain barrier, rather than direct infection of CNS. Hypocalcaemia and rise of transaminases observed in this patient may be partly due to dengue haemorrhagic fever and partly due to NMS.

The management of NMS has 2 components, supportive and specific. In suspicion of NMS, the likely medication should be withheld. Close monitoring as inpatients, ideally in a HDU or an ICU is needed. Our patient was managed in the HDU with cooling measures, fluid balance, maintaining haemodynamic stability .He didn't develop acidosis, myoglobinuria or renal impairment.

Metoclopramide is a recognized cause of neuroleptic malignant syndrome. Mainstay of treatment is withdrawal of the causative agent, supportive care with proper hydration aimed at maintaining haemodynamic stability and cooling measures along with specific treatment.

For patients who do not respond to withdrawal of medication and supportive care within the first 48 hours, the use of benzodiazepines, dantrolene, bromocriptine, and/or amantadine should be considered. However, these recommendations are based upon case reports and clinical experience, rather than from clinical trials. Their efficacy is unclear [8]. But as our patient was critically ill we started him on dantrolene within first 24 hours of diagnosis with marked improvement..

Electroconvulsive therapy (ECT) is considered in a small proportion in which residual catatonia persists.

Reintroduction of antipsychotic agents may or may not have a recurrent NMS episode. If antipsychotic medication is required, risk may be minimized by following some general guidelines which is generally done after 2 weeks.

Conclusion

NMS can only be diagnosed if considered paying detailed attention to history, symptoms, a careful neurological examination, and a high suspicion of causative agent. When it develops on top of another febrile illness, the diagnosis is further difficult.

Initial reports of mortality rates from NMS were over 30%, but reduced to almost 10% as a result of increased recognition and use of atypical antipsychotics. When recognized and treated early, majority of patients recover completely within 2 weeks. If not patients may take longer periods for recovery with residual neurological impairment. Sometimes death may occur as a result of renal failure, arrhythmia, DIC or cardiopulmonary complications.

Mainstay of treatment is withdrawal of the causative agent, supportive care with proper hydration aimed at maintaining haemodynamic stability and cooling measures along with specific treatment.

Informed written consent: Obtained

Acknowledgement

1. Dr.Upul de Silva, Consultant Physician, TH Karapitiya

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A septic cavernous sinus thrombosis secondary to orbital cellulitis and pan sinusitis complicated with subdural haemorrhage.

Case number : 04

Name of the Consultant : Dr.Upul de Silva

Name of the PGIM trainee : Dr.P.W.G. Chamika

Name of the patient :Mr.K.Munasinghe

Age :60 years

Ward number :19

Name of the Hospital :Teaching Hospital Karapitiya

BHT :170807

Date of admission : 14.11.2019

Date of discharge :13.12.2019

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Supervising Consultant

A septic cavernous sinus thrombosis secondary to orbital cellulitis and pan sinusitis complicated with subdural haemorrhage.

Abstract

Introduction Cavernous sinus is a dural venous sinus and thrombosis of this can be either septic or aseptic. Cavernous sinus is the most frequent dural sinus to become infected and thrombosed. Septic CST is an uncommon disease and carries a high mortality rate if not detected early and managed properly. Staphylococcus aureus is the commonest causative organism.

Case presentation A 60 year old male, with hypertension, diabetes, IHD and epilepsy presented with a severe right sided headache, fever, proptosis, ophthalmoplegia, and conjunctival chemosis of his right eye. He was drowsy with fluctuating level of consciousness. Right orbital cellulitis with CST was suspected. The laboratory workup and radiological assessment revealed a partial cavernous sinus thrombosis on right side and a left subdural haemorrhage with right orbital cellulitis and pan sinusitis. Blood culture and paranasal sinus aspirate were positive for MRSA, indicating that the orbital cellulitis is possibly due to an organism harboured in the sinuses. The patient was treated with appropriate antibiotics, surgical drainage of sinuses, hydration and glycaemic control. Anticoagulation was precluded due to the higher risk of expansion of the hematoma over potential benefits in the presence of a SDH. This case is one of the few cases reporting septic CST caused by MRSA, secondary to acute orbital cellulitis and pan sinusitis complicated with a SDH. The objective of this case report is to emphasize the importance of identification and proper management of a patient with a septic CST with haemorrhagic complications.

Conclusion In a patient with risk factors presenting with ocular symptoms suggestive of a CST, diagnostic imaging is a requisite. Administration of appropriate, broad-spectrum antibiotics entails the management, although anticoagulation and surgery are appropriate as adjunctive treatments in selected cases. Place for use of anticoagulation in management of CST in the presence of a SDH is controversial.

Key words case report, septic cavernous sinus thrombosis, orbital cellulitis, SDH

Introduction

The cavernous sinus is a dural venous sinus located on either side of the pituitary fossa and body of the sphenoid bone. It is in the posterior portion of the optic canal and superior to the orbital fissure. Through this traverse the internal carotid artery and cranial nerves III, IV, V, and VI [(1)]. It contains multiple trabeculae that act as sieves to trap bacteria, which results in the higher incidence of infection of the cavernous sinuses as compared with the other dural sinuses. Cavernous sinus thrombosis (CST) can either be septic or aseptic. Septic CST is when an infectious process triggers thrombophlebitis affecting the cavernous sinus and the structures traverse within. Aseptic CST is usually a thrombotic process that is a result of trauma, iatrogenic injuries, or prothrombotic conditions [(1)]. *Staphylococcus aureus* is the commonest organism causing septic cavernous sinus thrombosis and found in 70% of cases followed by *Streptococcus*, Gram-negative rods and anaerobes. *Aspergillus fumigatus* and mucormycosis are atypical causes of septic CST. The commonest primary site for septic CST is nasal furuncle (50%), followed by sphenoidal or ethmoidal sinuses sinusitis (30%) and dental infections (10%). The tonsils, soft palate, middle ear, and orbit (orbital cellulitis) are less common sites of primary infections to cause CST (listed in descending order of frequency)[(11)].

At the onset, symptoms of CST are not specific and the initial presentation would be mere headache with or without visual disturbance. It may precede fever and periorbital oedema[(12)]. Fever and the classic constellation of bilateral ptosis, proptosis, chemosis, and ocular muscle paralysis are present when there is apparent CST. However, the physical findings may be subtler at onset warranting a careful eye and neurologic examination, for an early detection. Periorbital oedema is an early sign. Exophthalmos and chemosis are a result from occlusion of the ophthalmic veins and generally occur just before or at the same time as ophthalmoplegia. Papilledema or dilated tortuous retinal veins are noted on fundoscopic examination [(12)].

This case is one of the few cases reporting septic CST caused by *Methicillin Resistant Staphylococcus aureus*, secondary to acute orbital cellulitis and pan sinusitis complicated with a subdural haemorrhage. The objective of the present report is to emphasize the importance of identification and proper management of a patient with a septic CST with haemorrhagic complications.

Time line

04.11.2019	Onset of severe, right sided, non-radiating headache, associated with fever, non-projectile vomiting, right periorbital pain and oedema
09.11.2019	Fluctuation in level of consciousness
14.11.2019	Hospital admission. Diagnosis of orbital cellulitis with suspected CST. Antibiotics started. X ray sinus view- B/L maxillary and frontal sinusitis.
16.11.2019	MRI brain with MRV revealed right orbital cellulitis with partial right cavernous sinus thrombosis and sinusitis of bilateral ethmoid & maxillary sinuses (Right> left) in addition to left side SDH
20.11.2019	Functional endoscopy with sinus washing was done. MRSA was positive in sinus aspirate. Antibiotics continued for 28 days.
13.12.2019	Patient discharged

Case Report Narrative

History

A 60 Y old farmer from a rural area of Sri Lanka, diagnosed to have hypertension, type 2 diabetes, IHD, migraine, and epilepsy got admitted with a severe, right sided, non-radiating headache, associated with fever, non-projectile vomiting, right periorbital pain and oedema for 10 days. He had fluctuations in his level of consciousness since 5th day of the illness.

He denied having cough, wheeze, ear discharge, history of head trauma, or drug overdose. He didn't have an epileptic attack during past 2 years. He had poor glycaemic control while on oral hypoglycaemic agents with a history of early cataract on left side, micro vascular (diabetic retinopathy, neuropathy, and nephropathy) and macro vascular (unstable angina and peripheral vascular disease) complications. He denied any allergies. His 10 year cardiovascular risk was 13.6%.

Examination

On admission, he was febrile with a temperature of 100^{o}F and dehydrated. He was drowsy with a GCS of 14/15.There were no signs of meningism. There was right peri-orbital oedema with erythema and tenderness, proptosis, complete ptosis and chemosis. He was not pale, icteric, or didn't have lymphadenopathy, rashes, or peripheral oedema.

Examination of nervous system revealed marked global external ophthalmoplegia of right eye without light perception in the same side. Visual acuity of his left eye was 6/60. Right pupil was dilated and sluggishly reactive. B/L fundoscopic examination revealed papilledema with proliferative diabetic retinopathy. Sensation over VI & V2 branches of 5th cranial nerve was impaired. Corneal reflex was absent on the right. Rest of the cranial nerve examination was normal. There was sinus tenderness and examination of ear, nose and throat has revealed rhinitic nasal mucosa. Motor examination of the upper and lower limbs was normal. He had peripheral glove and stocking type sensory impairment up to mid-thigh. There were no cerebellar signs.

His pulse rate was 98 bpm, and regular, with good volume and all peripheral pulses were present. His blood pressure was170/90 mmHg. S1 and S2 were normal in intensity without murmurs. JVP was not elevated. Respiratory examination revealed a respiratory rate of 18 cycles per minute, clear lung fields bilaterally with vesicular breathing pattern. Abdomen was soft, non-tender, not distended, with normal bowel sounds.

Differential diagnosis

The most likely differential diagnosis appreciated on initial presentation were an orbital infection such as orbital cellulitis complicated with meningitis, a cavernous sinus thrombosis (septic, aseptic), and mucormycosis. Malignancy (orbital, isolated sphenoidal tumours, rhabdomyosarcoma, secondaries), vascular abnormality (carotid aneurysm, carotid cavernous fistula, Tolosa hunt syndrome), inflammatory (sarcoidosis) causes, superior orbital fissure syndrome and orbital apex syndrome were less likely possibilities.

Diagnostic assessment

His WBC was 20970/UL with a neutrophil count of 16120/ UL, lymphocyte of 2360/UL, monocytes of 1490 /UL, haemoglobin of 8.5 g/dl, and platelet count of 421,000 / UL. Blood picture showed a neutrophil leucocytosis with toxic changes suggesting an infection and a normochromic normocytic anaemia.

Markers of inflammation were elevated with a CRP of 103mg/L and ESR of 127 mm in 1st hour. He had poor glycaemic control with a CBS of 311 mg /dL on admission.

S. Creatinine was 186 µmol/L and sodium and potassium were 134mmol/L and 3.7 mmol/L respectively. Serum corrected calcium was 2.35 mmol/L with S. phosphate 1.24 mmol/L and S. magnesium of 0.9 mmol/L. His INR was 1.05, and APTT was 33.2 s. Blood culture isolated MRSA.

NCCT brain revealed a subdural haemorrhage on left (find the image in the attachments). X-ray sinus view showed bilateral maxillary sinusitis (find the image in the attachments).

An urgent CE-MRI brain with orbital cuts was done under contrast prophylaxis with nephrology opinion as patient had renal impairment which revealed right orbital cellulitis with partial right cavernous sinus thrombosis and sinusitis of bilateral ethmoid & maxillary sinuses (Right> left) in addition to left side SDH (Figure 4,5).

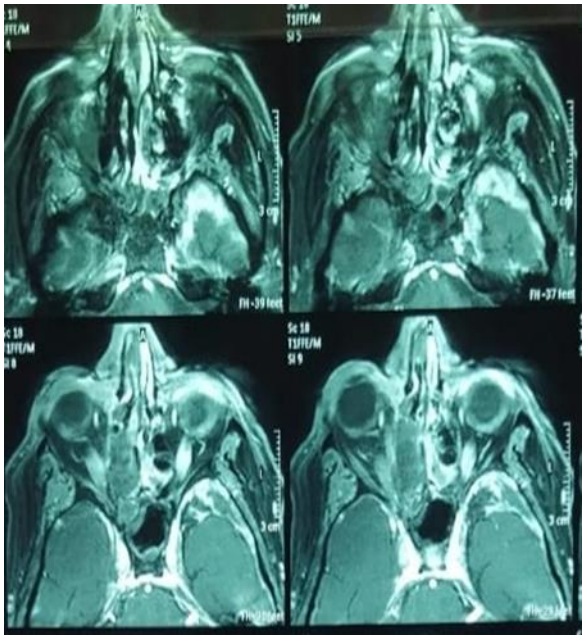

Figure 4: MRI brain with orbital cuts and sinus view showing right orbital cellulitis, pan sinusitis and cavernous sinus thrombosis.

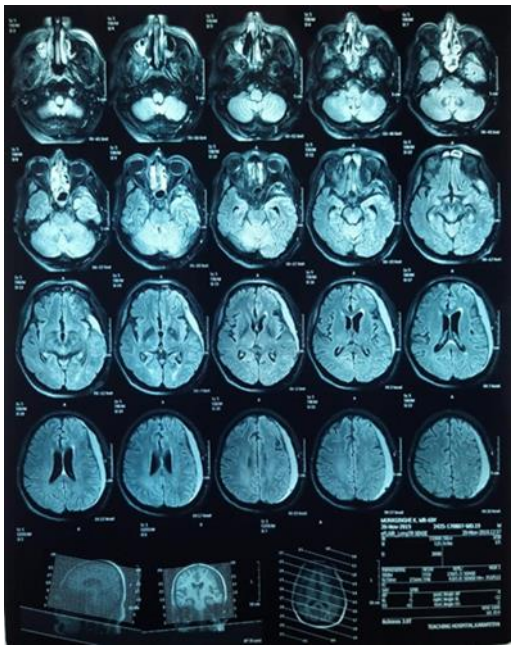

Figure 5: Left SDH on MRI brain of the same patient.

With the ENT opinion, functional endoscopy with sinus washing was done which revealed necrosed right anterior and posterior ethmoidal sinuses, with pus draining from right maxillary, sphenoidal and frontal sinuses. Pus and debris cleared, from all sinuses and aspirate was sent for culture. MRSA was positive in sinus washings, and sensitive to vancomycin. Fungal studies were negative for Aspergillosis and zygomycosis.

HIV was negative. Hepatitis B 's' antigen and Hepatitis C antibodies were negative. His 2D echocardiogram was normal with an ejection fraction of 60%. His SGOT was 24 U/L, SGPT was 43U/L, serum albumin was 30g/L with serum total protein of 64g/L. ALP was 98 U/L and FBS was 250 mg/dL. Melioidosis culture and antibody titre, Dengue antigen and antibody test, Rapid test, ELISA for leptospirosis, Mycoplasma antibody titre, and Brucella antibody were negative. No abnormality was detected in urine full report. USS abdomen showed increased cortical echogenicity of bilateral kidneys suggestive of an acute renal parenchymal disease and a grade 1 fatty liver. His chest radiograph was normal. Lactate was 2.1mmol/L, ABG showed compensated metabolic acidosis. Urine ketone bodies were negative. TSH was 1.1mU/L. CSF analysis was abandoned as patient had subdural haemorrhage. A summary of some important investigations are given below.

Date	**Investigation**	**Value**
14.11.2019	WBC	20.970 cells×10^9 /L
	Neutrophils	16.120 cells×10^9 /L
	Lymphocytes,	2.360 cells×10^9 /L
	Monocytes	1.490 cells×10^9/L
	Haemoglobin	8.5 g/dl
	Platelet count.	421× 10^9/L
	Blood picture	Neutrophil leucocytosis with toxic changes suggesting an infection

		and a normochromic normocytic anaemia.
	CRP ESR	103mg/L 127 mm in 1st hour
	FBS	250 mg /dL
	S. Creatinine Sodium Potassium UFR USS	186 µmol/L 134mmol/L 3.7 mmol/L Normal Acute renal parenchymal disease
	Serum corrected calcium S. phosphate S. magnesium	2.35 mmol/L 1.24 mmol/L 0.9 mmol/L
	INR APTT	1.05 33.2 s.
	Blood culture	isolated MRSA
20.11.2019	Para nasal sinus aspirate	Isolated MRSA Fungal studies - Negative
14.11.2019	SGOT SGPT Serum albumin with Serum total protein. ALP	24 U/L 43U/L 30g/L 64g/L 98 U/L
17.11.2019	2DE	Normal

Therapeutic interventions

General management with correction of dehydration with meticulous fluid balance, and glycaemic control with insulin was done. Soon after blood culture on admission, he was started on IV ceftriaxone 2 g bd and IV flucloxacillin 1 g 6 hourly empirically until the availability of culture reports. He was managed by a multidisciplinary team comprised of medical team, ophthalmologist, ENT surgeon, microbiologist, and neurosurgeon.

He was managed concentrating on his main acute problems which were orbital cellulitis, septic cavernous sinus thrombosis, pan sinusitis and acute on chronic SDH.

Orbital cellulitis was seen by the ophthalmology team and the patient has undergone removal of the upper and lower eye Iid inflammatory membrane surgically. G. moxifloxacin eye drops 4 hourly, G.tobramycin and dexamethasone eye drops 6 hourly, were started. After receiving the cultures, the antibiotics changed to IV vancomycin 1g daily and IV meropenem 1g bd.

The neurosurgical team decided to manage the subdural haemorrhage conservatively. Patient has undergone functional endoscopic sinus surgery (FESS) under general anaesthesia and clearance of debris and necrotic tissue was carried out. Para nasal sinus washing with normal saline was carried out. Nasal decongestant agents were started as supportive therapy. IV vancomycin 1g daily with IV meropenem 1g bd was continued for 28 days.

Because of the high risk of further expansion of SDH, subcutaneous enoxaparin was not started on this patient.

With treatment, his vision improved slightly and there was a marked reduction of orbital cellulitis with an improvement in inflammatory markers evidenced by an ESR drop to 32mm/1st hour, WBC dropping to 10400/UL and CRP to 2mg/dL. Repeated cultures were normal. His visual acuity didn’t improve completely due to bilateral proliferative diabetic retinopathy. He was referred to the vitreoretinal surgeon for further management. His renal functions normalized as the infection was settling.

Discussion

The cavernous sinus is in the posterior portion of the optic canal and superior to the orbital fissure. Through this traverse the internal carotid artery and cranial nerves III, IV, V, and VI. This anatomical relationship results in a group of clinical manifestations including ptosis, ophthalmoplegia, diplopia, and paraesthesia around the orbital cavity due to involvement of the eye motor nerves and impairment in the ophthalmic and maxillary branches of cranial nerve V when there is a thrombosis or an infection in the cavernous sinus[(1)]. Proptosis and chemosis block the drain from tributaries of superior and inferior ophthalmic veins as they directly drain to the cavernous sinus and further worsen them [(2)]. Cavernous sinus has complex anastomosis between the facial veins, the pterygoid plexus, and contralateral and intercavernous sinus. These connections explain how an infection in eye, sinuses or ear spread to the cavernous sinus and how an infection from one side spreads to the other cavernous sinus[(1)]. The cavernous sinus thrombosis could be either septic or aseptic. The septic focus is usually a pre-septal or orbital cellulitis, sinusitis or otitis media due to the characteristics of the veins and sinuses that lack valves and the close anatomical relationship of these structures to the cavernous sinus[(6)].

Clinical diagnosis is very important which can be confirmed radiologically. On non-contrast CT, thrombosis of the cavernous sinus is seen as an increased density. MRI brain with venogram is superior to CT scanning in detection of cavernous sinus thrombosis and MRI features suggestive include a heterogeneous signal from the abnormal cavernous sinus and hyper intense signal of the thrombosed vascular sinuses, along with deformity of the cavernous portion of the internal carotid artery.

According to one study, mortality outcomes have improved in the post antibiotic era from 100% to 20% after 1940,[(3)] and Yarington and colleagues have shown that there is a reduction of mortality from 50%-75% to 22% despite the complications and long term sequale [(4)]. Thus, appropriate

antibiotic treatment starting without delay is the mainstay of treatment and it should be continued for a minimum period of 3-4 weeks. *S. aureus* is the commonest to cause septic cavernous sinus thrombosis. However, broad-spectrum coverage for gram-positive, gram-negative, and anaerobic organisms should be started empirically and should include a penicillinase-resistant penicillin plus a third- or fourth-generation cephalosporin. If dental infection or other anaerobic infection is suspected, an anaerobic coverage should also be added.

There is controversy in use of anticoagulants in the treatment of cavernous sinus thrombosis. There is limited evidence to suggest that anticoagulants are probably safe and may be beneficial for people with sinus thrombosis [(7)] aiming prevention of further thrombosis and reduction of the risk of septic emboli. One review suggests that low-molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH). [(8)] However, in our patient, anticoagulants were contraindicated due to the presence of subdural haemorrhage. SDH is a recognized complication of cavernous sinus thrombosis as a result of increased venous pressure and therefore increased ICP [(9)] which was seen in our patient.

There are retrospective reviews suggest a possible decrease in mortality from 40% to 14% with UFH and reduction in neurologic morbidity, from 61% to 31% when anticoagulation is combined with antibiotics for septic cavernous sinus thrombosis. But there are no prospective studies supporting this.

When SDH arise from intracranial hypotension, as in our patient, the key treatment would be prevention of CSF leak, through epidural blood patches by treating the primary cause. The need for surgical evacuation should depend on the clinical circumstances and can be hazardous[(10)].

In the functional endoscopic sinus surgery, necrosed right anterior and posterior ethmoidal sinuses, with pus draining from right maxillary, sphenoidal and frontal sinuses were detected and pus & debris were cleared extensively. Neither fungal balls nor features of invasive mucormycosis were

detected. There was no histological evidence of mucosal invasion by the fungus on examination of the mucosal biopsy.

Conclusion

In a patient with risk factors presenting with ocular symptoms suggestive of a CST, diagnostic imaging with contrast-enhanced CT or MRI is a requisite. The administration of appropriate, broad-spectrum antibiotics entails the management, although anticoagulation and surgery are appropriate as adjunctive treatments in selected cases. This case shows the importance of a multidisciplinary approach for the management of orbital cellulitis. The place for use of anticoagulation in management of CST in the presence of a subdural haemorrhage is controversial.

Informed written consent: Obtained

Acknowledgement

1. Dr.Udaya Weerakoon Consultant Eye Surgeon, TH Karapitiya
2. Dr.S.A.Wickramasinghe Consultant ENT Surgeon, TH Karapitiya
3. Dr.Athula Dissanayaka, Consultant Neurologist, TH Karapitiya
4. Dr.N.Goonasekara, Consultant Neurosurgeon,TH Karapitiya
5. Dr.Bhagya Piyasiri, Consultant Microbiologist, TH Karapitiya
6. Dr.Upul de Silva, Consultant Physician, TH Karapitiya

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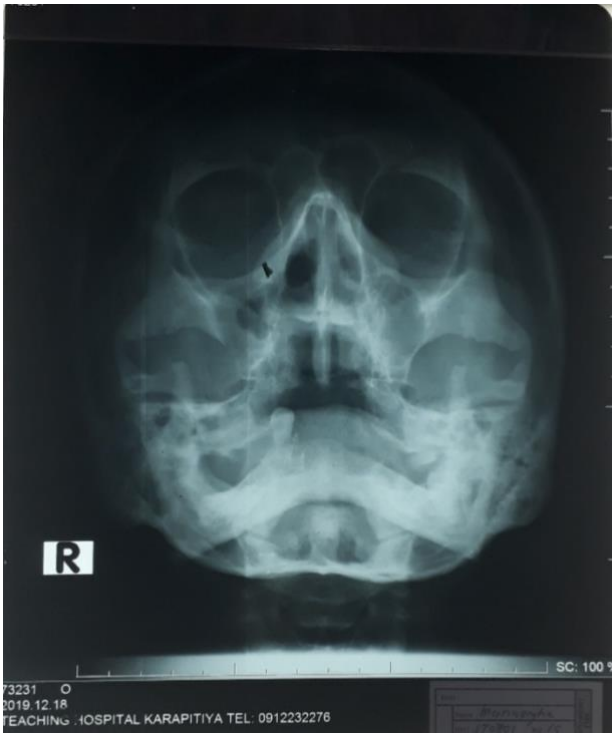
Attachment



Attachment 01: X-ray sinus view of the patient

Case number : 05

Name of the Consultant : Dr.P.P. Sathananthan

Name of the PGIM trainee : Dr.P.W.G. Chamika

Name of the patient :Mrs. K.P. Sumithra Damayanthi

Age :40 years

Ward number :39/ CCU- II

Name of the Hospital :Teaching Hospital Karapitiya

BHT :30290

Date of admission :26.02.2020

Date of discharge :13.03.2020

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Supervising Consultant

A case of triple vessel disease successfully treated with CABG during pregnancy

Abstract

Introduction Physiological changes in pregnancy results in increment of workload on the heart and precipitate pre-existing cardiac disease. Pregnancy itself is a risk factor for acute myocardial infarction (AMI). Typically, advancing maternal age and increased prevalence of associated comorbidity in pregnant population are the contributory causes for increased incidence of cardiovascular disease in pregnancy. IHD in pregnancy carries increased maternal and foetal morbidity and mortality risk.

Case presentation A 40y old patient with recently diagnosed IHD, presented in her 3rd pregnancy at POG of 10 weeks while awaiting further evaluation. After a coronary angiogram done at POA of 22 weeks showing triple vessel disease, she has undergone an on pump CABG at 24 weeks with favourable maternal and foetal outcome.

Conclusion Decisions on treatment options and timing of interventions should be taken depending on the maternal cardiac status and period of gestations by a multidisciplinary team. CABG during pregnancy carries high risk to the foetus though maternal outcome is similar to those of non-pregnant females.

Timing of surgery should be individualized and associated with minimal complications when done in second trimester, preferably between 20 to 28 weeks of gestation provided delay is not increasing maternal morbidity or mortality.

A pre-pregnancy counselling and cardiac assessment for women with advanced age that has fertility wishes, and advice regarding contraception in high risk population would reduce the prevalence of pregnancy complicated with ischemic heart disease in ideal setup.

Key words: case report, Pregnancy, CABG, triple vessel disease

Introduction

Pregnancy causes significant haemodynamic changes which include an increase in cardiac output by 30-40% in antenatal period which further elevates up to 80% in labour, increase of plasma volume by 50% and reduction in peripheral vascular resistance. The increase in cardiac output is a result of increasing the stroke volume and then from 28 weeks onwards by increasing the heart rate [1]. These changes increase the workload on the heart and precipitate worsening of any pre-existing cardiac disease.

In developed countries, cardiac disease complicates only 1-4% of pregnancies and it is the 3rd commonest cause for maternal death. In Sri Lanka, cardiac disease in pregnancy is due to 3 principle aetiology, naming rheumatic heart disease, congenital heart diseases, and ischemic heart disease. Heart disease in pregnancy is a major challenge to health care professionals with an escalation of maternal-foetal risks. Advancing maternal age and increased prevalence of comorbidities in pregnant population are the usual contributory causes for increased incidence of cardiovascular disease in pregnancy. Ischemic heart disease is not an absolute contraindication for pregnancy provided there is no severe symptomatic LV dysfunction <30%.

Ischemic heart disease in pregnancy should be investigated in the same manner as in the non-pregnant group. Maternal morbidity following AMI is high as a result of increased rates of heart failure, arrhythmia and cardiogenic shock.

Ischemic heart disease with acute coronary syndrome (ACS) is rare and most patients are managed medically or with percutaneous coronary intervention (PCI). Surgical revascularization in pregnancy is rare.

Delivery in women with history of AMI should be typically guided by obstetric indications.

This is a case of a 40 Y old patient recently diagnosed with stable angina, presenting with an unplanned pregnancy while on investigations and found to have severe triple vessel coronary artery disease (CAD). She has undergone an on pump CABG during the second trimester and delivered a full-term healthy baby at the end of 36 weeks.

Timeline

July 23, 2019	Diagnosed as having chronic stable angina .2DE showed mild LV dysfunction with EF of 50%.
Oct 11, 2019	Exercise ECG stage 1 positive
Dec 10, 2019	Pregnancy was confirmed by positive urine beta hCG.
Jan 17, 2020	Coronary angiogram was done at POA of 22 weeks which showed severe triple vessel disease with LMCA occlusion and dominant left system.
Feb 25 ,2020	Multi-disciplinary meeting on planning further management. Decision was to do on pump CABG.
Mar 03, 2020	CABG with LIMA graft to LAD was done at POA of 24 weeks.
Apr 20, 2020	Repeat 2 DE was normal.ef60%
Jun 01, 2020	Delivered a full term healthy baby at POA of 37 weeks by elective LSCS.

Case Report Narrative

History A 40 year old house wife, a mother of 2 children presented with progressively worsening exertional shortness of breath for 3 months.
She had mild exertional chest pain as well, which disturbed her household chores. Her symptoms of dyspnoea were of NYHA class I to II which relieved with rest. The associated chest pain was mild and central without association of autonomic symptoms or radiation. This was relieved immediately with rest. She denied having orthopnoea or paroxysmal nocturnal dyspnoea. There were no palpitations, presyncope or syncope. She didn't have reflux. She was not having fever at the moment or during recent past. There were no associated cough, wheeze or diurnal variation of symptoms.
After visiting the VP OPD clinic, she was referred to the cardiology clinic for further assessment. ECG was normal. A 2DE revealed an EF of 50% with mild LV dysfunction. She was scheduled for an exercise ECG and was started on medical management for chronic stable angina .Her exercise ECG was positive in stage one. She was scheduled for an coronary angiogram.In December 2019, she visited the clinic with a positive urine beta hCG report and a period of amenorrhoea (POA) of 10 weeks. Her LMP was 23.09.2019. She was previously apparently healthy and didn't undergo any surgeries in the past. She delivered 2 healthy babies through assisted normal vaginal delivery at term following uncomplicated antenatal period, 15 and 7 years ago

respectively. She denied having any allergies. She was a product of a non-consanguineous marriage and denied family history of IHD. She was not a smoker and was not exposed to passive smoking.

Examination She was thin built with a BMI of 18kg/m^2. She was not pale or icteric. There were no cyanosis, clubbing, bilateral ankle oedema or peripheral stigmata of infective endocarditis. Her pulse rate was 88bpm, regular and normal volume. Blood pressure was 120/80 mmHg and JVP was not elevated. S1 & S2 were heard in normal intensity. There were no added sounds or murmurs. Respiratory examination was normal and there was no evidence of heart failure clinically. Her SpO_2 % was 98% on room air. Abdominal examination was clinically unremarkable.

Diagnostic assessment

Her ECG was normal. A 2D Echocardiogram done before the pregnancy, in October 2019 revealed a mild ischemic LV dysfunction with apico-septal, apical and anterior wall hypokinesia. This was repeated in December 2019 at POA of 14 weeks which showed similar results. The exercise ECG (before pregnancy) was strongly positive in stage I with aVR ST elevations.
In February 2020, at 22 weeks coronary angiogram was done which revealed following results.

LMCA	Mild tubular stenosis.
LAD	70% ostial plaque. 99% plaque at D1 D1 large vessel 90% plaque proximally
Circumflex artery	Large, dominant, 99% ostial plaque. Another 99% lesion involving origin of OM -1 OM-1- Large vessel, ostial 99% lesion; graftable.
RCA	Non dominant. Severe diffuse disease, 99% lesion in the mid segment.
Conclusion	Severe triple vessel disease with LMCA involvement. Dominant left system
Recommendation	1. Surgical revascularization. **2.** A multidisciplinary team meeting regarding care of this pregnancy and delivery.

Troponin was normal, total cholesterol 190, triglycerides 74, low density lipoprotein (LDL) 126 and high density lipoprotein (HDL) 40. FBS was 98mg/dL. Her serum creatinine was 0.66mg/dL.

Her FBC was normal with a WBC of 10,000/UL, neutrophil 65%, Haemoglobin 11g/dL, platelet 221,000/UL. ESR was 20mm in 1st hour and CRP was <6mg/L. AST and ALT were normal. TSH was 1.6mU/L and normal.

USS revealed a single live foetus with regular cardiac pulsation and foetal movements were noted. Placenta was extending posteriorly to fundus.

Therapeutic intervention

A multidisciplinary meeting was held in February 2020 regarding the treatment options for this patient. This team included cardiologists, physician, obstetrician, anaesthetist, and cardiothoracic surgeon.

On pump CABG was done under general anaesthesia on 03/03/2020, at POA of 24 weeks. LIMA graft to LAD, left Saphenous Vein Graft (SVG) to D_1 and circumflex artery was done achieving a good flow. Post-operative period was uneventful.

Follow up

She was reviewed in cardiology clinic again at a POG of 31 weeks with development of bilateral pitting ankle oedema and repeated 2DE in April,

2020 showed improvement of EF to 60% with no RWMA, (LVEDD was 46mm LVESD was 28mm). A mild TR noted.

She was continued on aspirin 75mg nocte, clopidogrel 75 mg nocte, rosuvastatin 5mg nocte and carvedilol 6.25mg bd.

Clopidogrel was withheld at 36 weeks of POG and a live male child weighing 2.4 kg was delivered by LSCS at 37 weeks of gestation. Post natal period was uneventful.

Discussion

Being a developing country with low health expenditure compared to many developed countries, health indicators of Sri Lanka are impressive and are comparable to many developed countries. Women with pre-established coronary artery disease, mainly atherosclerotic coronary artery disease carry the highest risk adverse cardiac events during pregnancy. The reported maternal mortality in above cases is as high as 0 to 23%. Adverse foetal or neonatal outcome is observed in 30% of cases [2].

According to WHO risks of contraception and pregnancy in heart disease published in 2006, pulmonary arterial hypertension (maternal mortality 17-50%), severe symptomatic LV dysfunction (LVEF<30%, NYHA III-IV), previous peripartum cardiomyopathy with any residual impairment of LV function, severe mitral stenosis, severe symptomatic aortic stenosis, Marfan syndrome with aortic dilatation > 45mm, aortic dilatation > 50mm associated

with bicuspid aortic valve and native severe aortic coarctation are considered as class IV diseases where patients should be advised against pregnancy, and if become pregnant, termination is considered. In the above Modified WHO Classification of Maternal Cardiovascular Risk, our patient was categorized under category II–III with moderate increase in maternal mortality morbidity risk as she had mild LV impairment which is not an absolute contraindication for pregnancy. Apart from advanced maternal age, she did not have other traditional risk factors for coronary artery disease. In contrast to many patients with IHD associated with pregnancy, she was not obese and in fact had a low BMI at presentation. ECG and measurement of troponin levels are recommended when a pregnant woman has chest pain (I C)[3].This patient presented with an unplanned pregnancy while on the investigations for IHD. However, in these type of scenario, diagnostic workup must be individualized with consideration of the potential maternal and foetal risk [4].

Cardiac surgery carries a high-risk of maternal and foetal morbidity and mortality. When maternal mortality rates with CABG comes down to that level of the non-pregnant population, foetal mortality remains to be elevated (16% to 33%) [5]. Thus, extreme caution should be taken in choosing patients who undergo cardiac surgery during pregnancy. Such indications would be acute decompensation with medical treatment fails or less invasive therapeutic means or emergency (thrombosis or valvular dysfunction, endocarditis, dissection of the aorta, intra-cardiac tumour embolism, and unstable angina) [6]. Maternal morbidity and mortality are strongly correlated with functional

status. Our patient was not having significant functional limitation to start with and had only NYHA class I to II symptoms with an EF of 45% to start with. The management should be based on a multidisciplinary approach including the cardiologist, obstetrician, cardiac surgeon, anaesthetist and physician. Even when indicated, optimal timing of cardiac surgery is a critical decision to make. Early intervention will decrease maternal risk but may result in foetal demise. In contrary, delaying cardiac surgery until after delivery may result in maternal death. The maximum cardiac output during pregnancy is observed in 20 to 28 weeks of gestation.

According to available literature, for IHD patients diagnosed at the beginning of pregnancy that require CABG during pregnancy, best timing for CABG is the second trimester. As surgery done in the first trimester has risk of miscarriage and foetal malformations and in the third trimester has the risk of preterm labour [7]. Cardiopulmonary bypass adversely affects placental perfusion as a result of non-pulsatile blood flow and hypotension and, this leads to disturbances in organogenesis and influences foetal outcome. Increased foetal mortality is related with increased cardiopulmonary-bypass time. Foetal mortality was also related to a longer anoxic time.[7] CABG in pregnancy must be performed at high flow, high pressure, in normothermia and with the shortest possible extracorporeal circulation time. Off-pump coronary artery graft in experienced hands is associated with reduced foetal mortality rates when compared to cardiopulmonary bypass procedure due to continued pulsatile blood flow to the foetus .This is recommended as an

alternative approach when technically feasible. Although cardiopulmonary bypass carries a high risk during pregnancy, utilizing high flow, high pressure, pulsatile, normothermic bypass, with foetal and uterine monitoring during procedure minimizes associated risks [(8)].

Timing of delivery should be individualized. If CABG is planned or delayed until 28 weeks of gestation, both LSCS and CABG can be done at the same time as improved neonatal care increases the chances of neonatal survival [[7]].

If there are no other obstetric indications, vaginal delivery was preferred.

Conclusion

Management decisions in IHD in pregnancy should be taken by a multidisciplinary team of cardiologist, obstetrician, anaesthetist and cardiothoracic surgeon.

CABG during pregnancy carries high risk to the foetus though maternal outcome is similar to those of non-pregnant females.

Timing of surgery should be individualized and associated with minimal complications when done in second trimester, preferably between 20 to 28 weeks of gestation provided delaying surgery is not increasing maternal risk for an adverse cardiovascular event.

A pre pregnancy counselling and cardiac assessment for women with advanced age who have fertility wishes, and advice regarding contraception in

high risk population would reduce the prevalence of pregnancy complicated with ischemic heart disease in ideal setup.

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