Pseudallescheria boydii Lung Infection in an Immunocompetent Adult, Difficulties in Diagnosis and Management


Abstract

Pseudallescheria boydii and its asexual state Scedosporium apiospermum is a well known opportunistic pathogen among immunocompromised patients. However it is rare in immunocompetent patients. The optimum management of this infection is still not clear. We report a case of Pseudallescheria boydii lung infection in an immunocompetent patient who had an old tuberculous cavity and presumed inhalational exposure. The case highlights difficulties in diagnosis which complicates the selection of antifungal agent/s and the need for aggressive surgical debridement.

Introduction

Pseudallescheria boydii and its asexual state Scedosporium apiospermum is rare in immunocompetent patients, though its well known in immunocompromised hosts. The optimum management of this infection is still not clear. We report a case of Pseudallescheria boydii lung infection in an immunocompetent patient who had an old tuberculous cavity and presumed inhalational exposure. The case highlights difficulties in diagnosis which complicates the selection of antifungal agent/s and the need for aggressive surgical debridement.

Case Report

VP, a 27 years old male had pulmonary tuberculosis 15 years ago and received treatment for 6 months, currently working in a warehouse. He presented with fever, cough and hemoptysis for last 3 months. Chest imaging revealed a left upper lobe cavity with fungal balls and surrounding areas of consolidation and bronchiectasis. The lower lobes were normal. The patient underwent a left upper lobectomy. Histology of the resected lung was now ready and identified the fungus as Pseudallescheria boydii. The patient continued to remain sick. He agreed to a left lower lobectomy at this time. At surgery a small pinhole and a blackish area was found at the stump. A dramatic improvement in his clinical condition occurred after surgery. He completed 6 weeks of antifungal therapy and was discharged. The report from the reference laboratory was now ready and identified the organism as Pseudallescheria boydii.

Discussion

Pseudallescheria boydii is a saprophyte found in stagnant water and soil and can be acquired by trauma, barrier breaks, aspiration of soil or swamp water or working in sewers. Our patient was immunocompetent, but was working in a warehouse and had an old tuberculous cavity. This could have got infected by the inhalational route. Culture media used by most clinical laboratories do not support formation of the Pseudallescheria state. However, by convention the name of the sexual state Pseudallescheria boydii has priority over the name of the asexual state Scedosporium apiospermum. The hyphae of Pseudallescheria boydii are narrower, have irregular septations and the ends of hyphae as well as intercalary septae show bulbous swelling. These features are said to distinguish Pseudallescheria boydii from Aspergillus, but the distinction is very difficult in practice. From therapeutic point of view, however precision in the mycological diagnosis is required as each fungus has different antifungal drug susceptibility. Besides the diagnosis needs to be available in a suitable time frame. Delays in diagnosis may lead to inappropriate treatment with grave consequences especially in the immunocompromised patient. In this case, presumed Aspergillus was treated with itraconazole and presumed Fusarium was treated with voriconazole. When Mucor could not be ruled out, amphotericin B was started as it is the only effective agent against it, but Pseudallescheria is almost always resistant to it. Combinations with amphotericin B, fluconazole or terbinafine have an indifferent effect against Pseudallescheria whereas combinations including an azole such as itraconazole, voriconazole, posaconazole or ravuconazole and an
Pseudallescheria boydii swelling. These features are said to distinguish phase of reaction). Detailed medical history of systemic hypereosinophilia and hypogammaglobulinemia (in early fever, maculopapular rash, generalized lymphadenopathy, and immunotherapeutic agents etc. It usually presents with aromatic anticonvulsants, some antibiotics, antiviral, it is rare but a severe type of drug reaction, most commonly with aromatic anticonvulsants, some antibiotics, antiviral, and immunotherapeutic agents etc. It usually presents with fever, maculopapular rash, generalized lymphadenopathy, hypereosinophilia and hypogammaglobulinemia (in early phase of reaction). Detailed medical history of systemic medications plays a central role. Before making the diagnosis, some antifungal agents which have to be reviewed in the light of better antifungal agents which target the fungus and its susceptibility more precisely.

**Discussion**

Pseudallescheria boydii is a saprophyte found in stagnant water and soil and can be acquired by trauma, barrier breaks, aspiration of soil or swamp water or working in sewers. Our patient was immunocompetent, but had an old tuberculous cavity which got infected by the inhalational route. Culture media used by most clinical laboratories do not support formation of the Pseudallescheria state. However, by convention the name of the sexual state Pseudallescheria boydii has priority over the name of the asexual state Scedosporium apiospermum. The hyphae of Pseudallescheria boydii are narrower, have irregular septations and the ends as well as intercalary septae of hyphae show bulbous swelling. These features are said to distinguish Pseudallescheria boydii from Aspergillus. But the distinction is very difficult in practice. From therapeutic point of view, however precision in the mycological diagnosis is required as each fungus has different antifungal drug susceptibility. Besides the diagnosis needs to be available in a suitable time frame. Delays in diagnosis may lead to inappropriate treatment with grave consequences especially in the immunocompromised patient. In this case, presumed Aspergillus was treated with itraconazole and presumed Fusarium was treated with voriconazole. When Mucor could not be ruled out, amphotericin B was started as it is the only effective agent against it, but Pseudallescheria is almost always resistant to it. Combinations with amphotericin B, fluconazole or terbinafine have an indifferent effect against Pseudallescheria, whereas combinations including an azole such as itraconazole, voriconazole, posaconazole or ravuconazole and an echinocandin such as caspofungin, micafungin or anidulafungin exhibit synergy against Pseudallescheria.

While the critical role of surgery in management is undisputed, it has significant morbidity. The need for extensive surgery may have to be reviewed in the light of better antifungal agents which target the fungus and its susceptibility more precisely.

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**References**


**Carbamazepine Induced DRESS Syndrome**

**Abstract**

We present here an 18yr old male who presented with intermittent fever of moderate grade and of 15 days duration, followed by maculopapular erythematous rashes over upper and lower extremities, face, and trunk developing over 10-12 days. He was suffering from recurrent seizures since last 3 months for which he was started on carbamazepine 200mg twice daily for the past 6 weeks. He was febrile on admission. Generalized lymphadenopathy with discreet, non-matted, firm and tender inguinal lymph nodes. Patch test with 1% and 5% solution of carbamazepine was strongly positive.

**Introduction**

DRESS syndrome is a drug hypersensitivity syndrome which begins around 2-6 weeks after exposure to a drug. It is rare but a severe type of drug reaction, most commonly with aromatic anticonvulsants, some antibiotics, antiviral, and immunotherapeutic agents etc. It usually presents with fever, maculopapular rash, generalized lymphadenopathy, hypereosinophilia and hypogammaglobulinemia (in early phase of reaction). Detailed medical history of systemic medications plays a central role. Before making the diagnosis, other eosinophilic disorders like rhinitis, asthma, allergic hypersensitivity reactions, hypereosinophilic syndrome, eczema, Well syndrome, eosinophilic fasciitis, pulmonary diseases (Churg-Strauss, eosinophilic pneumonia), eosinophilic gastroenteritis, malignancies (Hodgkins lymphoma, myeloproliferative disorders), and parasitic infestations should be ruled out. Here we present a rare case of DRESS syndrome due to carbamazepine.

**Case Report**

An 18yr old male engineering student, resident of Chikmagalur, presented with intermittent fever of moderate grade and of 15 days duration. This was followed by maculopapular erythematous rashes over upper and lower extremities, face, and trunk developing over 10-12 days. There were bullous eruptions on soft palate also, since one week. Patient gave history of suffering from recurrent seizures since **Physician, Department of Medicine, “Resident, Department of Medicine, “Pathologist, Department of Pathology, “Deputy Chief of Medical Services and Head-Department of Medicine, Senior Physician, Department of Medicine, HAL Hospital, Bangalore 560 017, India. Received: 28.01.2010; Revised: 23.03.2010; Accepted: 09.04.2010**
ANA, pANcA, cANcA and rheumatoid factor were negative.

not reveal any growth. Antibodies against dengue - negative.

parasite was not seen, blood culture and urine culture did

5.10mcg/ml (4 - 8mcg/ml)

Globulin- 3.00 g/dl.(2.0 -3.0g/dl). Sr. carbamazepine level-

examination: No ova and cysts. Serum protein electrophoresis:

routine showed 1-2 pus cells per HPF with no rbcs seen. Stool

days of treatment. Kidney function tests were all normal. Urine

tests showed raised serum transaminase levels (ASt 153 and

Westergren’s) and Platelets – 2.37lakhs/cmm. Liver function

31/12/09 (post treatment) was normal.

showed normocytic, normochromic rbcs, leucocytosis, atypical

features were suggestive of drug hypersensitivity changes.

Skin biopsy: showed epidermis with acanthosis and features of focal interface dermatitis. There was a sub epidermal perivascular inflammatory aggregate composed of small lymphocytes, histiocytes and numerous eosinophils. All these features were suggestive of drug induced skin changes.

Bone Marrow: Eosinophilic precursors were markedly increased (24%).lymphoid cells were also increased (12%).

Investigations

On admission his total leukocyte counts were 25,400 with 41% eosinophils with absolute eosinophil count- 5460/cmm. After stopping carbamazepine and treatment with steroids for 10 days total leukocyte count dropped to a normal value of 8300 with 2% eosinophils. Peripheral smear (on admission) showed normocytic, normochromic RBCs, leucocytosis, atypical lymphocytosis and eosinophilia. Repeat peripheral smear on 31/12/09 (post treatment) was normal.

Hb -13.8gm%, ESR: 10mm (at the end of first hour by Westergren’s) and Platelets – 2.37lakhs/cmm. Liver function tests showed raised serum transaminase levels (AST 153 and ALT 178) on admission, which again became normal after 10 days of treatment. Kidney function tests were all normal. Urine Routine showed 1-2 pus cells per HPF with no RBCs seen. Stool examination: No ova and cysts. Serum protein electrophoresis:

- Total protein – 6.8g/dl (6.4-8.3), Albumin: 3.8(3.9 -5.1)g/dl, Globulin- 3.00 g/dl.(2.0 -3.0g/dl). Sr. Carbamazepine level-

5.10mcg/ml (4 - 8mcg/ml)

HBsAg, HIV, WIDL and VDRL were all negative, malarial parasite was not seen, blood culture and urine culture did not reveal any growth. Antibodies against dengue - negative. ANA, pANcA, cANcA and rheumatoid factor were negative. Heterophile antigen test for infectious mononucleosis and IgM/

IgG for EBV were both negative.

USG abdomen showed mild hepatosplenomegaly, X-ray chest PA view was normal. MRI brain was also normal

EEG showed slow wave activity with high amplitude wave pattern at 3 – 4 Hz/sec.

Lymph node biopsy: showed diffuse hyperplasia with polymorphic cellular infiltrate composed of small lymphocytes, histiocytes and numerous eosinophils and paracortical postcapillary venular hyperplasia. All these features were suggestive of drug hypersensitivity changes.

Skin biopsy: showed epidermis with acanthosis and features of focal interface dermatitis. There was a sub epidermal perivascular inflammatory aggregate composed of small lymphocytes, histiocytes and numerous eosinophils. All these features were suggestive of drug induced skin changes.

Bone Marrow: Eosinophilic precursors were markedly increased (24%).lymphoid cells were also increased (12%).

Treatment

We treated our patient by first discontinuing anti convulsant-carbamazepine. To control the seizure we started patient on topiramate 50mg b.d. and clobazam 10mg b.d. following which patient did not have any seizures. Since it is reported that if a patient is sensitive to one aromatic anticonvulsant similar reaction can be seen with another aromatic anticonvulsants (namely phenytoin and phenobarbinate, we used topiramate and clobazam). Patient was also started on i.v. betamethasone and hydroxyzine for his generalized severely pruritic skin eruptions. Skin rashes, mucosal bullous eruptions and other haematological investigations including total counts, eosinophil counts, and liver function tests improved remarkably in 10 days. There was a reduction in the number of palpable lymph nodes following treatment. Overall clinical condition improved and patient was discharged after tapering and stopping steroids. Topiramate and Clobazam were continued.

Patch Test: Patient was called for follow up visit 2 months after he was discharged and a patch test with 1% and 5% solution of carbamazepine (Figs. 1, 2) was strongly positive (2+ according to ICDRG grading).

Discussion

DRESS (drug rash or reaction with eosinophilia and systemic symptoms) syndrome begins 2-6 weeks after exposure to a drug. This term was introduced in 1996 by Bocquet et al. It appears acutely in first 2 – 6 weeks after initiation of therapy [Kim C W et al., 2006]. Although rare, it is seen with lots of commonly used drugs like phenobarbinate, carbamazepine, phenytoin, lamotrigine, minocycline, sulphonamide, allopurinol, dapsone, ethambutol, celecoxib, etc. It is important to recognize this entity early because it can mimic other pathologies; is potentially
Tilting at Windmills

Yash Lokhandwala¹, Mandar Shah², Gopi Krishna Panicker³

Abstract

A 69-year-old man had numerous episodes of syncope over three years. A head-up tilt test had shown a mixed response and he was labeled as having neurocardiogenic syncope. Lifestyle, dietary and pharmacologic measures were ineffective. At electrophysiology study, an easily inducible, self-terminated AV nodal re-entrant tachycardia was induced. At 1 year follow-up after radiofrequency ablation, he is asymptomatic.

Introduction

The head-up tilt test is a common diagnostic procedure in the investigation and classification of syncope. However, its lack of specificity can be a stumbling block in the effective management of syncope. We present such a case in which the tilt test wrongly classified syncope as neurocardiogenic.

Case Report

In July 2008, we saw a 69-year-old man who had numerous episodes of syncope and near-syncope, since 3 years. The syncope was preceded by abrupt rapid palpitations. Sometimes the palpitations occurred without accompanying syncope, especially while supine. The physical examination was normal. He had no diabetes or hypertension. There was no family history of sudden cardiac death. He had been subjected to many investigations, many of them more than once. The results of cardiac investigations like the standard 12-lead, 24 h-ambulatory electrocardiograms (ECGs), echocardiography and coronary angiography were normal. A tilt-table test, conducted in 2007 had shown a positive “mixed” response after provocative testing using sublingual isosorbide dinitrate, with a drop in his blood pressure (BP) followed by sinus bradycardia and near-syncope.

Based on this, he was diagnosed to have neurocardiogenic syncope and advised lifestyle and dietary modifications, which he meticulously followed. But despite all this, he continued to have frequent episodes of near-syncope or syncope. Further neurological evaluations, including a magnetic resonance imaging-brain evaluation were also normal. Treatment with atenolol also proved ineffective.

We reviewed the history. Since the episodes were preceded by abrupt rapid palpitations just prior to the syncope and were not associated with any nausea, vomiting or sweating, we considered an arrhythmic etiology. We therefore subjected him to an electrophysiology study. This revealed supraventricular tachycardia (SVT), which was inducible repeatedly with atrial extra-stimuli. The SVT started with an atrial-His (AH) jump and revealed simultaneous activation of the atria and the
Discussion

The most common causes of syncope are neurocardiogenic, orthostatic hypotension and underlying arrhythmias. Upto 25% of syncope is caused by tachyarrhythmias. AVNRT is not typically thought of as an arrhythmia associated with syncope, although some reports cite a history of syncope in as many as 20% of patients. The mechanism of syncope associated with SVT is multifactorial, due to vasomotor compensatory responses, possible induction of vasovagal reactions, including the body position during the tachycardia and the use of medications (antiarrhythmic drugs, vasodilators, etc.).

This case also draws attention to the serious problem that tilt-table test can cause in the effective management of syncope. It emphasizes that the present schema for the evaluation and management of syncope is an expensive model. The average patient with syncope makes 10.2 visits/year to a physician and sees an average of 3.2 specialists for the problem, with the cost per diagnosis being significantly high depending on the tests performed and the diagnostic accuracy. The evaluation of a case of syncope necessarily starts with a detailed history, the physical examination and ECG to determine the possible cardiac etiology. When these tests are normal, most algorithms gravitate towards the tilt-table test as the next step in the evaluation of syncope.

While the tilt-table test is helpful in determining an individual's susceptibility to syncope, it does not fully duplicate the exact type, intensity, or duration of the provocative stimuli encountered in normal life. Consequently, in regard to the ECG findings documented during spontaneous syncopal events, tilt-table testing appears less able to correlate the heart rhythm responses observed during induced and spontaneous episodes. A tilt-table test yielding a positive response in patients with structurally normal heart indicates neurocardiogenic syncope as the most likely diagnosis. In the present case, the tilt-table test similarly resulted in the presumptive diagnosis of neurocardiogenic syncope.

This case illustrates that a “positive” tilt test considered in isolation can easily lead the physician up the garden path. A detailed analysis of the history cannot be overemphasized in determining the etiology of syncope. An over-reliance on the tilt-table test will only result in physicians ‘tilting at windmills’ in the treatment of syncope. In the same context, a detailed analysis of the history cannot be overemphasized.

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Scintigraphic Finding of a Silent Hepatic Haemangioma

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Abstract

Hepatic haemangioma is the most common benign tumour of liver. Most of them remain asymptomatic and are detected incidentally. Tc 99m RBC blood pool imaging is highly specific diagnostic modality of choice for hepatic haemangioma as its hypervascular nature may createequivocal result on CT or MRI. The sensitivity and specificity increases using SPECT especially in lesion less than 2 cm. Therefore all patients suspected of having hepatic haemangioma should undergo Tc 99m blood pool imaging.

Introduction

Hemangiomas are congenital vascular malformations arising from arteries, veins, capillaries and called as
almost 100% & is considered as a frontline diagnostic modality of choice.

**Case Report**

55 year old gentleman met with an minor accident resulting in multiple right ribs fractures. His subsequent investigations incidentally detected a hepatic mass lesion on USG abdomen. He was asymptomatic as such. His general physical examination was unremarkable. Systemic examination did not reveal any such tenderness in right hypochondriac region or hepatomegaly. His investigation profile reveals normal haemogram with Hb = 13.2 gm/dl, TLC = 6,050/cmm and platelet = 3,00,770/ul. His liver function test reveals total bilirubin = 0.8 mg/dl. To elaborate more on mass lesion with mixed echogenicity seen on USG abdomen, MDCT abdomen with contrast was done which reveals a hypodense mass lesion in posterior segment of right lobe of liver measuring 8.5 x 9.6 x13.0 c.m. in size extending beyond lower border of liver into hepatorenal fossa causing mild displacement of right kidney (Figure 4a). It shows characteristic central enhancement in post-contrast study (Figure 4b, Figure 4c). Though it is highly suggestive of cavernous haemangioma differential diagnosis includes focal nodular hyperplasia, fibrolamellar Carcinoma cyst. To clarify the nature of lesion, Tc $^{99m}$ RBC blood pool imaging is asked for by the treating gastroenterologist. In vivo labelling of RBCs was done with prior injection of stannous pyrophosphate, following 20 min later, injection of Tc $^{99m}$ pertechnitate is administered keeping patient under a large field view of dual head E-cam Gamma Camera fitted with parallel hole leap collimator. Images were acquired in anterior, posterior projections. These reveal a well circumscribed area of perfusion defect (cold area) seen in all dynamic images as well as in immediate post static scan (Figure 1, Figure 2b). On the static delayed blood pool images, there was gradual accumulation of tracer in the said lesion showing uniform uptake pattern as that of rest of the hepatic parenchyma consistent with haemangioma of liver (Figure 3).

**Discussion**

Hepatic haemangiomas are the most common benign tumour of liver. It is a congenital vascular malformation growing in size with growth of liver. The incidence rate varies from 0.5 to 7 %. Though they occur in both sex, female shows preponderance with Male: Female = 1:4. Female preponderance could be explained by the fact that oral contraceptive, steroid, HCG, clomiphene citrate, pregnancy causes growth of hepatic haemangioma. Histologically it is an endothelium lined vascular channel with fibrous septations. Their growth is by ectasia but never by neoplasia. Incidental detection suggest their asymptomatic nature but if at all symptomatic it is in 3rd to 5th decade largely.
Fig. 4a: Plain MDCT of liver shows hypodense lesion in posteroinferior segment of right lobe of liver

Fig. 4b: Arterial Phase reveals mild degree of incomplete peripheral enhancement.

Fig. 4c: Venous Phase reveals further increase in the peripheral enhancement.

Fig. 4d: Delayed scan shows uniform central pooling of contrast agent, rendering it almost isodense with rest of the liver parenchyma.

Clinical features include dull aching right hypochondriac pain, abdominal fullness, hepatomegaly and rarely acute pain due to thrombosis. Complications are exceedingly rare and largely depend on size. These include rupture of haemangioma. CCF due to AV shunting, gastric outlet obstruction, thrombocytopenia with coagulopathy, lower limb edema with ascites due to pressure on IVC may precipitate.

High sensitivity & specificity of non-invasive radiologic tool in diagnosis of hepatic haemangioma has definitely obviated the need of liver biopsy and also bypassed the danger associated with it. The various imaging modalities include USG, CT with contrast, Tc\(^{99m}\) labelled blood pool study, MRI. Though USG is most common initial diagnostic modality it has low sensitivity of 46%. Also the appearance of hepatic haemangioma on USG is highly variable and non-specific. A 3-Phase CT scan (arterial/venous/portal) with delayed imaging has a sensitivity of 69%. Though sensitivity of MRI ranges from 82-96% it often fails to differentiate between hypervascular neoplasm or focal nodular hyperplasia from haemangioma.\(^2\)\(^3\) However Tc\(^{99m}\) labelled RBC blood pool study has sensitivity of 82% & specificity of almost 100%. On RBC blood pool study haemangioma shows decreased perfusion followed by delayed filling classically referred to as perfusion blood pool mismatch. The mismatch is produced due to sluggish blood flow through haemangioma relative to surrounding normal tissue despite of increase in blood pool. For the lesion less than 2 cm, Tc\(^{99m}\) RBC SPECT scores better over planar Tc-99m RBC blood pool study.

As most of them are asymptomatic and as they never turn malignant they may be left alone safely.\(^6\) There is no known medical treatment for it. Surgical treatment is indicated in rupture, large haemangiomas with considerable pressure symptoms and Kasabatch–Merritt syndrome\(^7\) where hepatic haemangioma are associated with thrombocytopenia and intravascular coagulation. Surgical modalities include resection, enucleation, arterial embolisation, radio frequency ablation, orthotopic liver transplantation. But surgical resection and enucleation are the preferred treatment of choice.

References

Experience with Patients with Anti-MUSK Antibody Positive Myasthenia Gravis

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Abstract
The association of muscle tyrosine kinase (Musk) antibody with recurrent bulbar weakness in acetylcholine receptor antibody (Ach-R Ab) negative myasthenia gravis (MG) has been well documented. We describe 2 patients, a middle aged man and a 9 year old girl, both seronegative for Ach R antibody who had recurrent bulbar weakness and MUSK antibody positivity. Patients made a full recovery from the acute episode with intravenous immunoglobulin (IV Ig) therapy. The peculiar clinical features of this condition and its management are discussed.

Introduction
Antibodies to muscle acetylcholine receptor are present in roughly 85% of patients with generalized myasthenia gravis and 50% of patients of pure ocular symptoms. Up to 70% of Ach R negative myasthenia patients (seronegative myasthenia gravis) have antibodies to muscle specific tyrosine kinase (Musk). This antibody is specific for a form of myasthenia gravis that, although quite rare, has no other diagnostic serum marker. This entity needs to be considered in the differential diagnosis of patients with unexplained recurrent weakness, especially if the weakness involves bulbar and ocular muscles.

Case Report 1
A 54 year old man presented with one month history of progressive dysphagia to both solids and liquids, hypo nasality of voice, nasal regurgitation of fluids, followed by mild drooping of bilateral eyelids. These symptoms were worse in the evening.

He had been diagnosed to have myasthenia gravis in 2005, when he had presented with bulbar symptoms. Investigations then had revealed acetylcholine receptor antibody to be negative, decremental study on low rate RNS to be positive from deltoid and nasalis and CT chest to be normal. He had been on Acetyl cholinesterase inhibitors [Pyridostigmine 60 mg four times daily] and tapering dose of prednisolone [5 mg once daily at this presentation] since then.

Clinical examination revealed patient to be afebrile with normal vital parameters and normal respiratory rate. He had bilateral mild ptosis, full extra ocular movements, weak gag bilaterally, decreased palatal movements, with curtaining of palate and a nasal voice. Attempted swallowing of 15 ml of water resulted in nasal regurgitation and wet cough. Mild facial, neck and proximal muscle weakness were present, with all deep tendon reflexes being present. A few crepitations were heard in the right infraclavicular and mammary areas. There were no cholinergic signs and symptoms – viz. pulse rate was 84/min, pupils were 3 mm reactive, there was no evidence of increased respiratory secretions and bowel movements were normal.

Routine hematological and biochemical investigations were normal. Chest X Ray revealed a right upper lobe consolidation. Thyroid function tests were normal. High resolution computerized tomography (HRCT) revealed a large area of consolidation [9x7x4.5 c.cm] with evidence of irregular cavity [5x2.3 x 2.4 c.cm] containing multiple hypo dense non-enhancing areas within, suggesting necrosis. The margins of this consolidation were spiculated. Few sub centimeter sized lymph nodes were noted in the pretracheal regions. These findings suggested either infective etiology or neoplasm.

Anti – MUSK antibody was done in this patient in view of recurrent bulbar weakness in a case of acetylcholine receptor antibody negative Myasthenia Gravis. Anti – MUSK Antibody was positive[0.76 nmol/L] [Ref < 0.05].

Patient was administered amoxicillin plus clavulanate intravenously and serial sputum samples for detection of acid fast bacilli were sent. He was put on naso-gastric feeding. Patient received intravenous immunoglobulin over a 5 day period.

Over the next 2 weeks, gradual improvement was noted. At the end of 2 weeks, swallowing function was normal and ryles tube could be safely removed. Ocular, bulbar and facial weakness had completely resolved. Patient continued to be afebrile. Sputum for acid fast bacilli were negative and repeat Chest X Ray showed almost complete resolution of the consolidation. The patient was discharged at the end of 20 days on acetylcholinesterase inhibitors, prednisolone 20mg and azathioprine 50mg.

Case 2
A 9 year old girl presented with recurrent bulbar and ocular weakness and mild proximal limb weakness of 5 years duration. She had been diagnosed to have seronegative myasthenia gravis (positive decremental response from deltoid and nasalis) 5 years ago. The patient had been on acetylcholine esterase inhibitors at a dose of 30 mg four times daily with 10 mg of prednisolone
daily. Despite therapy, she required 2 cycles of intravenous immunoglobulins and ventilatory support twice, over a 2 years period, for recurrent bulbar weakness. At the second admission, anti-MUSK antibody was done and reported to be 0.48 nmol/l (≥0.5 nmol/l). At the last admission for bulbar weakness, she was managed with intravenous immunoglobulin. Thymectomy has been planned for her in view of recurrent crises requiring immunotherapy.

**Discussion**

The first patient presented with worsening of bulbar symptoms while on treatment for myasthenia gravis. The possibilities considered were – cholinergic symptoms causing muscle weakness, an intermittent pulmonary infection / pulmonary neoplasm worsening underlying myasthenia, and anti-MUSK antibody positive myasthenia gravis.

Cholinergic crisis was unlikely in view of lack of any associated muscarinic symptoms. The lack of high fever or leucocytosis in presence of lung consolidation could be explained by ongoing steroid therapy, possibility of infection being tuberculosis or possibility of pulmonary neoplasm underlying the consolidation. The latter was likely as the patient had been a smoker in the past. Oat cell carcinoma of the lung which frequently involves the apical tissue may be associated with Lambert–Eaton myasthenic syndrome (LEMS). The clinical and electrophysiological features in this patient did not support a diagnosis of LEMS.

Although bronchoalveolar lavage was planned in this patient towards investigation of pulmonary neoplasm, it was not carried out due to rapid improvement of pulmonary signs and resolution of consolidation on repeat chest X Rays.

The second patient had onset of symptoms at 5 years of age. The peculiar problem of immunotherapy and thymectomy at this age, offered fresh challenges in her management. Anti – MUSK positive myasthenia gravis typically presents in young females between 10 and 40 years of age. However, 1 in 8 patients is male. Patients often present with bulbar and ocular weakness but profound neck and respiratory weakness without other signs may occur. Limb and axial symptoms which may be present in the acute phase of the disease, may remit with treatment while facial and bulbar weakness persist.3

MUSK is a transmembrane polypeptide expressed selectively in skeletal muscle and in Torpedo electric organ. Its extracellular region contains four immunoglobulin like domains and cysteine rich domain; its intracellular region is made of a juxtamembrane domain, a kinase domain and a C-terminal tail. MUSK is part of a receptor for agrin, a nerve – derived protein which is essential for neuromuscular synapse formation (Liyang et al., 2002).4 Although agrin MUSK interaction is not fully understood, experimental data show that agrin activation of MUSK through tyrosine phosphorylation leads to clustering of selected muscle proteins, including acetylcholine receptors and to acetylcholine receptor phosphorylation.

When the MuSK -antibody test is positive, it is a useful diagnostic indicator of MG in Ach R antibody-negative patients with generalized myasthenic weakness. Musk antibody positivity rate, as reported by Zhou et al,5 was 40% in patients with generalized MG with Ach R antibody negativity. Testing for musk antibody should be performed before initiation of immunosuppressant therapy.

In a study of anti-MUSK Antibody in Seronegative MG by Evoli et al, 47.4 % of Seronegative MG were detected to have anti- MUSK antibody. The clinical picture corresponded to oculo-bulbar form of myasthenia, comprising a severe disease with involvement of vital areas such as bulbar and respiratory muscle. In Zhou et al’s series, Extra-ocular muscle involvement has been shown to be comparable in musk antibody positive and negative patients (60% and 73% respectively).3 Ach R antibody positive patients too have a comparable incidence of extracutaneous muscle involvement5. Involvement of respiratory and bulbar muscles (seen in 20% and 30%5 patients respectively) has been shown to be slightly higher in MUSK antibody positive patients as compared to MUSK negative patients, in Zhou’s series. MUSK antibody positive group has been shown to have a higher incidence of neck muscle weakness during the course of the illness , involving either neck extensors or flexors or both. Limb weakness, however, has been shown to be more common in antibody negative group (100%) as compared to MUSK antibody positive group (60%).3

Initial reports by Evoli, Padua et al described facial muscle weakness or atrophy in Musk positive patients. However this feature was not confirmed in Zhou et al series. In their study only 50% of Musk antibody positive patients developed mild facial weakness.

Single fibre electromyogram (EMG) is the most sensitive investigation in the electrophysiological evaluation of seronegative, MUSK positive MG. RNS from limb muscle may be positive in less than 60% of the cases. Up to 30% of MUSK positive patients show equivocal or negative reaction to edrophonium/ neostigmine injection. Chronic administration of pyridostigmine may cause more side effects than remission of weakness. Hence the diagnosis of Seronegative MG especially in MUSK positive patient, may present peculiar difficulties.

In the present case, the marked bulbar weakness mandated therapy with intravenous Immunoglobulins to prevent further worsening and development of life-threatening respiratory weakness. A literature search did not yield guidelines on management of respiratory or bulbar crisis specific to anti MUSK positive MG. In a series by Zhou et al, responses to antiacetylcholinesterase inhibitor and immune-modulatory agents were similar in MUSK-antibody positive and negative groups, with 30% in the former, and 53% in the latter, responding to pyridostigmine. As their study was retrospective, the responses of the two patients groups to individual immunomodulator therapy could not be compared. However, virtually all the patients were treated with and responded well to various combinations of immunosuppressant agents including prednisone, azathioprine, cyclosporine, mycophenolate, intravenous immunoglobulin, plasmapheresis and high dose cyclophosphamide. Evoliz et al and Sandars et al have reported similar response to corticosteroid, cyclosporin A, and azathioprine.5,6 Thus, current clinical experience suggests that the immunosuppressive agents currently used for acetylcholine receptor antibody positive MG, are also effective in anti MUSK antibody positive or negative MG.

However high dose immunosuppressive therapy may not prevent frequent disease deterioration requiring emergency treatment.5,6 Additionally, many patients may develop permanent cranial and bulbar weakness over the years. The role of thymectomy, mycophenolate or high dose cyclophosphamide remains to be determined.

**References**

Kikuchi Fujimoto Disease and Systemic Lupus Erythematosus - A Rare Association

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Abstract

Kikuchi Fujimoto disease is rarely associated with systemic lupus erythematosus (SLE). Kikuchi Fujimoto disease may precede, follow or coincide with the diagnosis of SLE. We report a case who was initially diagnosed as Kikuchi Fujimoto disease with SLE. She is presently in remission after treatment of SLE.

Introduction

Kikuchi Fujimoto disease is an inflammatory disorder of lymph nodes characterized by necrotizing lymphadenitis. It is a rare and usually self-limiting disease. It is a distinct clinicopathological entity of unknown etiology. Kikuchi Fujimoto disease can be associated with SLE, Sjogren’s syndrome, Still’s disease or Sweet’s syndrome. Such an association is rare and important as the clinical course, management and prognosis of patient with Kikuchi’s disease with SLE differs from patient with simple Kikuchi Fujimoto disease.

Case Report

A 39 year old woman presented with complaints of multiple joint pains not associated with swelling, since 3-4 years involving both small and large joints of both upper and lower limbs. She had developed erythematous nodules over both the lower limbs since 8 months. There was no history of photosensitivity, morning stiffness, malar rash, dry mouth or difficulty in getting up from squatting position since 6 months. There was no history of excessive hair loss since 8 months and difficulty in getting up from squatting position since 6 months. She gave history of recurrent oral ulcers, joint pains not associated with swelling, since 3-4 years involving both small and large joints of both upper and lower limbs. She had developed erythematous nodules over both the lower limbs in different stages of resolution. There were no history of photosensitivity, morning stiffness, malar rash, dry mouth or difficulty in getting up from squatting position since 6 months. There was no history of excessive hair loss since 8 months and difficulty in getting up from squatting position since 6 months. She gave history of recurrent oral ulcers, excessive hair loss since 8 months and difficulty in getting up from squatting position since 6 months. There was no history of photosensitivity, morning stiffness, malar rash, dry mouth or Raynaud’s phenomenon. There was no history of tuberculosis in the past. Her menstrual history was normal and there was no history of spontaneous abortions.

Two years ago, she was admitted to another hospital for evaluation of cervical lymphadenopathy. Excision biopsy was suggestive of histiocytic necrotizing lymphadenopathy [Kikuchi Fujimoto disease (KFD)] and she was treated symptomatically. Prior to the present admission, she was being treated with steroids, hydroxychloroquine and methylxate for three months as suffering from rheumatoid arthritis. There was no improvement when she was seen at our hospital.

On examination her pulse and blood pressure were normal. She was pale. Skin examination showed mildly tender, palpable, erythematous nodules, non-pruritic, less than 0.5 cm in diameter over both the lower limbs in different stages of resolution. There was a right cervical 2 cm non-tender and firm lymphnode situated in the posterior triangle. Oral cavity and fundus examination were normal. Muscle power was grade 4/5 in the proximal muscles of both lower limbs. Upper limb power was normal. On investigation, hemoglobin was 9.1gm/dl, peripheral smear showed normocytic normochromic anemia, WBC and platelet count were normal. Serum creatinine was 1.1mg/dl (normal 0.5-1.5 mg/dl), liver function tests, ultrasonography of the abdomen and X-ray chest were normal. Antinuclear antibody (ANA) and double stranded DNA (dsDNA) were positive in the titres of 1:100 speckled pattern and 1:640 respectively by immunoflorescence, C3 complement level was 50 mg/dl (normal 80-177 mg/dl), C4 complement level was 12 mg/dl (normal 15-47 mg/dl). Serum creatine phosphokinase (CPK) level was 1248 IU/L, ESR was 24 mm at the end of one hour. Moun tox test was negative. HIV-ELISA was nonreactive. Urine examination showed no proteinuria. Direct Coombs test was positive. Fine needle aspiration cytology of the cervical lymphnode was suggestive of non-specific lymphadenitis. Serology for Epstein Barr virus (EBV), cytomegalo virus (CMV), parvo virus B19, human herpes virus-6 (HHV-6), and toxoplasma could not be done. She was diagnosed to suffer from SLE and was treated with prednisolone 1 mg/kg/day for 6 weeks with gradual tapering dose to a maintenance dose of 5 mg/day, hydroxychloroquine 200 mg twice daily, folic acid 5 mg/day and photoprotection. With treatment the patient improved clinically. At 3 months follow up the lymph nodes regressed completely. Presently she is asymptomatic and in remission at follow up of 1 year duration.

Discussion

KFD is an inflammatory disorder involving the lymph node. It was first described as subacute necrotizing lymphadenitis by Kikuchi and Fujimoto separately in 1972. It is usually a self-limiting benign disease, mainly seen in Asian females between 30-50 years and improves within four months but recurrences have been reported.

KFD is associated with various connective tissue disorders like Sjogren’s syndrome, SLE, Sweet’s syndrome, and Still’s disease and skin disorders like psoriasis.1,2 The association of KFD and SLE is interesting as there is a clinical and histologic overlap between the two diseases. KFD has been considered as SLE-like disorder due to a strong immunological response to a viral antigen. Lymphadenopathy is a frequent and usually a non-specific feature of SLE. It has been reported in 12-59% of patients in SLE but it is rarely a presenting feature.3 SLE patients with lymphadenopathy usually have higher disease activity levels.4 Excision biopsy of the lymph node is necessary for histological diagnosis. Histologically it may be difficult to differentiate disorders at neuromuscular junction. Muscle Nerve 2002;25:4-16.


between SLE and KFD. The lymph node shows presence of hematoxyline bodies, abundant plasma cells and true vasculitis outside the area of necrosis in SLE. There is encrustation of blood vessels with nuclear dust (Azzopardi phenomenon) seen in KFD associated with SLE. It has been suggested that it may be a forme fruste of SLE. Neutrophils are absent or rare in KFD which is a feature of SLE.

Usually KFD is self-limiting, but fatal outcome in association with SLE has been reported. Early and intensive immunosuppression is the treatment for patients with KFD who develop serious complications. KFD can precede, follow or coincide with the diagnosis of SLE. Hence patients with KFD should be assessed for SLE and followed up regularly. KFD should be ruled out in patients with SLE flare up with lymphadenopathy because of risk of fatal outcome of KFD in association with lupus.

Corticosteroids are useful for both KFD and SLE. Recent studies have shown that minocycline, ciprofloxacin, chloroquine and hydroxychloroquine are also useful in the treatment of KFD.

References

Serious Neutropenia following Etanercept Administration in a 62 Years Female Patient of Rheumatoid Arthritis

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Abstract
Tumor necrosis factor (TNF) plays an important role in the inflammatory process of RA and the resulting joint pathology. Etanercept is a member of anti TNF family which is indicated in patients with moderate to severe active rheumatoid arthritis either alone or in combination with MTX. Very few cases of neutropenia with etanercept treatment have been reported worldwide so far. The mechanism of etanercept induced neutropenia is not yet established. We report a case of 62 year female patient, developing etanercept induced neutropenia after 1 month of starting treatment. The absolute neutrophil count (ANC) came down to 150/µl on the 6th day of diagnosis. Bone marrow examination revealed a maturation arrest of granulocytic cells. Other marrow components were normal. Causality assessment of adverse drug reactions was done as per Naranjo’s Algorithm. It was a probable ADR. We propose the possible mechanism of neutropenia is bone marrow toxicity. This is contrary to a previous case report which suggested peripheral consumption of neutrophil as a cause of neutropenia. Recently, there are some reports of leukemia and other hematological malignancies associated with the use of etanercept and in those conditions neutropenia could be the first manifestation. Neither product label of the drug nor US FDA warns for periodic blood investigation during etanercept therapy. There is a definite need for total and differential count estimation at the beginning and regular interval during etanercept treatment to rule out possibilities of neutropenia.

Introduction
Rheumatoid arthritis (RA) is a systemic autoimmune disorder involving chronic synovial inflammation of multiple large and small joints and progressive joint damage which may lead to irreversible joint damage with disability and deformity. This joint inflammation is a result of the excessive production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-1, IL-6 by activated T cells and the stimulation of immunoglobulin production by B cells. TNF plays an important role in the inflammatory process of RA and the resulting joint pathology. Elevated levels of TNF have been reported in the synovial fluids of patients of RA. Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. It is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderate to severe active rheumatoid arthritis either alone or in combination with MTX. Most common side effects during etanercept treatment include dizziness, headache, pain, redness, upper respiratory infection itching and swelling at injection site. Some of the serious side effects include tuberculosis, multiple sclerosis, rare reports of serious blood problems, heart failure and immune

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reactions and hematological malignancies. Very few cases of neutropenia with etanercept treatment have been reported so far from clinical trials and practices.

### Case Report

We report a case of a 62 year female patient who developed etanercept induced severe neutropenia after 1 month of starting treatment. The patient was suffering from poorly controlled progressive rheumatoid arthritis for last 5 years. She was having bilateral inflamed painful, tender knee, ankle joints along with Z deformity in upper extremities. She had signs of disease progression in spite of having regular treatment of prednisolone, (0.5 mg/kg/day), methotrexate (15mg orally/week) for last 2 years. The patient was concurrently receiving folic acid (5mg/week) during the course of methotrexate therapy. Etanercept was added in place of methotrexate which was withdrawn following suspected hepatotoxicity. All the hematological parameters (Hemoglobin, MCH, MCV, MCHC RBC count, total WBC count, Differential count, platelet count) were within normal range during the course of Methotrexate therapy as well as at the time of its stoppage due to hepatotoxicity. The patient received twice weekly subcutaneous injections of 25mg etanercept for a period of 4 weeks. After 4 weeks of starting new regimen (etanercept+ prednisolone) the patient came to clinic complaining of gingival pain and swelling. On examination it was found to be a case of gingival abscess but the typical signs of inflammation like fluctuation, tenderness and redness were less prominent.

Suspecting some bacterial infections routine blood counts and blood culture were ordered. Blood culture report did not show any growth. The CBC picture of blood was total WBC count 2900/µl, absolute neutrophil count 930/µl, Hemoglobin 12.3 gm/dl, RBC 4.3 x 10^{6}/mm^{3}, MCH 27.3 pg/cell, MCV 86.4 fl, platelet count 175 x 10^{3}/mm . Monitoring of the WBC count was started on a daily basis. On the subsequent 6th day, the total leucocyte count (TLC) was 1250/µl and the absolute neutrophil count (ANC) came down to 150/µl. Hemoglobin and platelets values remain unchanged. Bone marrow examination was ordered to establish the cause of neutropenia which revealed maturation arrest of granulocytic cells. Other marrow components were normal. Etanercept was stopped immediately after getting the hematological report suspecting a drug induced neutropenia. Cytogenetic analysis was done to rule out possibilities of acute myeloid leukemia (AML) as there was previous report of etanercept induced AML. Neupogen (Filgrastim) Granulocyte stimulating factor (G-CSF) was started at 300 µg per day subcutaneously for 12 days. Neutrophil count started improving and reached 3000/µl on 18th day. Causality assessment of adverse drug reactions was done as per Naranjo’s Algorithm. It was a probable ADR. Rechallenge with etanercept was not done.

### Discussion

The authors rule out this case as Methotrexate induced bone marrow toxicity since there was no hematological abnormalities at the time of stoppage of Methotrexate and during its course. The Methotrexate induced bone marrow toxicity is generally mild leucopenia and mostly occur in elderly patients with diminished folate storage. Elevation of mean corpuscular volume (MCV) usually precedes the occurrence of hematological toxicity due to methotrexate. The mild bone marrow suppression responds to drug withdrawal for 2 weeks. Our patient had normal folate storage and developed Neutropenia after 4 weeks of treatment stoppage of Methotrexate. The Mean corpuscular volume (MCV) was within normal range at the time of neutropenia. So in all probabilities this is a case of etanercept induced Neutropenia.

There are very few reports of etanercept induced neutropenia worldwide. Most of adverse drug reactions reported in Indian patients receiving etanercept were skin rash, rhinitis, injection site reactions and eczema.In the previously reported etanercept trial amongst Indian patients, a patient developed neutropenia after 52 days (8 weeks) of initiation of etanercept which was attributed to the development of systemic lupus erythematosus. The patient we were treating developed neutropenia after 4 weeks of starting of treatment without any clinical manifestations and blood features of SLE (antinuclear antibody negative). The cause of etanercept induced neutropenia has not yet been established. In another reported incidence of etanercept induced neutropenia, the probable reason for neutropenia suggested was due to peripheral neutrophil consumption. In our study, we found in the bone marrow examination maturation arrest of granulocytic cells suggesting possible marrow toxicity. Hence, further study is required to establish the exact cause of etanercept induced neutropenia. The diagnosis of bone marrow suppression due to etanercept in this patient is supported by many facts: first, the patient was not receiving any other medications which could produce neutropenia when bone marrow suppression was noticed. Second, the neutrophil counts returned towards normal within a few days after discontinuation of the suspected drug and initiation of Neupogen (Filgrastim).

The typical features of inflammation and infection are often missing in the patients of severe neutropenia. The product level of the drug or US FDA does not specifically ask for periodic total and differential blood counts during etanercept therapy. These could lead to either missing or delaying the diagnosis of etanercept induced neutropenia. Recently, there are some reports of leukemia and other hematological malignancies associated with the use of etanercept and in those conditions neutropenia could be the first manifestation. Hence, there is a definite need for total and differential count estimation at the beginning and regular interval during anti TNF treatment.

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