Case Report

PUO Due to Langerhans Cell Histiocytosis

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Abstract

Langerhan Cell Histiocytosis (LCH) is a disorder in which cells with a phenotype similar to that of epidermal langerhans cells cause tissue damage possibly through excessive cytokine production. The clinical spectrum of the disease is wide. We are reporting a case of LCH who presented with prolonged pyrexia and a clinically benign bony swelling of mandible of long duration, which was otherwise ignored as being unrelated. The biopsy from the swelling confirmed the diagnosis of LCH. Another biopsy from lower end of tibia where he had pain also demonstrated typical findings. There was no evidence of other system involvement. There was good remission of the swellings and the symptoms with steroid alone initially but later relapsed and is now on treatment as per LCH III protocol. The case is being reported for its rarity and for the unusual presentation as PUO.

INTRODUCTION

Langerhan cell histiocytosis (LCH) is a rare disorder. It is not a malignancy even though chemotherapeutic agents are used in its treatment with varying success. The clinical spectrum of the disease is wide and multi system and single organ involvement is possible. The behaviour and response to therapy are unpredictable. It is still an orphan disease and PUO as a manifestation is probably rare.

CASE REPORT

A 46 years male, a bank employee who was apparently well until one year back, was admitted with complaints of fever of one year duration, bony swelling on the right side of the jaw close to the angle of mandible of more than one year duration and pain in the right leg above the ankle joint of two weeks duration. His complaints started as low grade fever manifesting as evening rise of temperature. Episodes of fever lasted for 2-3 days and were relieved spontaneously or by antipyretics at times. For the past two months fever was present on all most all days. No history of loss of weight, cough with hemoptysis, arthralgia, bone pain, rashes, photophobia, high-risk sexual behavior, occupational contact with animals and bleeding manifestations. There was no history of change in bowel or bladder habits or polyuria. He noticed a swelling on the right side of the outer aspect of the jaw close to the angle of mandible even six months before the onset of fever, which was painless. Swelling gradually increased in size but for the past few months it had remained static and did not bother him much. Swelling was not associated with pain, except when pressed hard. No neurological or vascular compromise due to the swelling. He noticed pain in the right lower limb, just above the ankle joint two weeks back. He had slight difficulty in walking due to the pain. No history of swelling in other parts of the body. He was a known diabetic for the past six years on dietary control alone. No past history suggestive of pulmonary tuberculosis or inflammatory joint disorders.

On examination he was moderately built and nourished. No pallor or lymphadenopathy. Pitting edema of the right ankle was present. There was a bony swelling on the lateral aspect of the right jaw close to the angle of mandible, 4x3 cm, hemispherical in shape with smooth surface and hard in consistency. Skin over the swelling appeared normal. On palpation there was no local warmth and it was non-tender.

On systemic examination, respiratory system revealed normal respiratory movements with bilateral vesicular breath sounds. Alimentary system revealed no abnormalities. Cardiac and CNS examination were within normal limits.

Before the referral to Calicut Medical College he was investigated extensively as a case of Fever of Unknown Origin but the results were inconclusive. Investigations done in our institution were X-ray of the mandible followed by biopsy from the swelling, which gave the diagnosis. Subsequently another biopsy was done from right tibia when he developed pain there whilst under observation, which also was typical of LCH.


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Platelet count: 400,000/cumm. Peripheral smear revealed mildly hypochromic microcytic RBC with no immature cells and no parasites. Serum electrophoresis revealed no M band. Serum uric acid was 5.5 mg/dl. Tuberculin test was negative. ANA, anti ds DNA and Rheumatoid factor were negative. Brucella antibody was negative. Liver enzymes and renal functions were normal. Chest X-ray was normal.

USG Abdomen revealed no abnormal findings. X-ray of the mandible revealed an osteolytic lesion on the right side. X-ray of the right ankle revealed multiple lytic lesions in the lower end of tibia. Biopsy was taken initially from the mandible and the report came as “fibrocollagenous tissue and sheaths of histiocytes with oval or indented nuclei intermingled with scattered eosinophils, and osteoclastic type of giant cells seen in the periphery- typical of Langerhans cell Histiocytosis. Biopsy from the lower end of the tibia also demonstrated similar histopathological findings. Initially we thought of conservative management with reassurance and observation, as there was no other system involvement. But when he developed the painful lesion in the right tibia he was started on Prednisolone at a dose of 1mg/ Kg/day, to which there was prompt response. Both mandibular swelling and the tibial lesions disappeared but he required oral hypoglycemics to control his
diabetes. He was on alternate day steroid but while attempting to taper the steroid he developed new lesions in the lower ends of the femurs on both sides and had to be considered as progressive multifocal bone disease and treatment as per LCHIII regime was given to which there was satisfactory response and presently being followed up.

**DISCUSSION**

Fever as a complaint lasting for six months or for more than a year is a relatively uncommon problem and are due to:

1. Exaggerated circadium rhythm
2. Factitious fever
3. Thyrotoxicosis, Granulomatous hepatitis, Still’s disease,
4. Rarer isolated causes like Brucellosis, Lymphoma, or still rarer conditions

In such prolonged fevers documentation that the patient has fever or not should be the first step and to identify it as organic or not based on the associated symptoms and signs and studying the psychosocial aspects of the patient. Always exclude thyrotoxicosis in such patients. Langerhans cell Histiocytosis is a very rare disorder considered as an Orphan disease. It is still rarer for it to present as PUO

Langerhans Cell Histiocytosis(LCH) is a disorder of unknown etiology in which cells with a phenotype similar to that of epidermal langerhans cells cause tissue damage, possibly through excessive cytokine production. Langerhans cells are derived from hemopoietic stem cells in the bone marrow, which then migrate from the blood to the skin. They are powerful antigen presenting cells and an exaggerated cytokine response may explain most of the clinical and pathological features of LCH. Current ideas on pathogenesis implicate either an altered, dysfunctional population of langerhans cells or an abnormal population of T cells producing trophic cytokines, which attract normal langerhans cells to sites of tissue involvement.\(^4\)\(^6\) 99% of cases are sporadic; peak age at presentation is 1-2 years but with a range from birth to old age. Males are affected twice as commonly as females. Single system disease affects the skeleton, skin, lungs or lymph nodes in decreasing order of frequency. Painful swellings of virtually any bone is the most common presenting feature and adjacent soft tissues or overlying skin or mucous membrane may be involved. Well-defined osteolytic lesions are typical but peristomal reaction may be prominent and mimics the appearance of malignancy. The spleen is often enlarged. Lung disease may be the only manifestation of langerhans cell histiocytosis in adults. In young children lung involvement may be symptomless but tachypnea and rib recession are often seen. The earliest radiological abnormalities are interstitial shadows that cavitate, forming microcysts. As the cysts enlarge bullae form and may rupture causing pneumothorax. Lungs may become small and stiff with reduced total lung volume and decreased compliance. Diagnosis is confirmed by finding LCH cells in the bronchial washings or by lung biopsy. In the central nervous system the pituitary, stalk and hypothalamus are most commonly involved and diabetes insipidus is the most common presentation.\(^5\)

Cases have been reported where the presentation was in the form of adult onset epilepsy.\(^3\)

**Management**

Based on LCH III treatment guidelines cases are divided into three groups

1. Multisystem high risk
2. Multisystem low risk
3. Single system with multifocal bone disease
4. Localised special site involvement.

**Single system disease:** Spontaneous resolution of bony lesion is common and a period of observation is appropriate. Painful or unsightly lumps may require intervention and intralesional corticosteroids (20-80 mg or methylprednisolone) is usually effective. Bony lesion that are inaccessible and might compromise vital organs may require treatment with low dose irradiation. Single
lymph nodes can be excised. Painful polyostotic disease of massive lymphadenopathy usually responds to a short course of corticosteroids.

**Multisystem disease:** Symptomless patients may be managed by careful observation with a real chance of spontaneous resolution. Where systemic treatment is required cytotoxic drugs and corticosteroids either alone or in combination has been regarded as standard treatment, but no particular regimen has been shown to be superior. Vinblastine and etoposide are most often used, usually alone or with a steroid. Cyclosporin, interferon-alpha, 2-chlorodeoxyadenosine and allogenic bone marrow transplant have been used for nonresponders.1,2,6

The patient under discussion belonged to the third group that is progressive multifocal bone disease and there was inadequate response to standard protocol with Vinblastine and Prednisolone. The treatment protocol for this patient as per LCH III guidelines was initial treatment of six weeks and a continuation treatment of twelve months. The initial treatment consisted of continuous oral prednisolone (40mg/m² in three divided doses) for 4 weeks tapered over next two weeks plus weekly Vinblastine(6mg/m²) for six weeks and Methotrexate (500mg/m²)infusion with folinic acid rescue on weeks 1, 3 and 5. Continuation treatment is started in patients who respond to the initial treatment and is to be given for twelve months with 6MP(50mg/m²) and weekly Methotrexate(20mg/m²) with pulses of oral Prednisolone and Vinblastine every three weeks. The patient has undergone treatment initially with Vinblastin and Prednisolone alone but was not responding and after starting Methotrexate there was good response and is on continuation treatment with 6MP and weekly Methotrexate.

Late sequelae: The outlook for patients with single system disease is excellent with minimal long-term sequelae though the course is unpredictable in some. However majority of patients will have multisystem disease without organ dysfunction. Mortality in this group is low but half are likely to have long-term morbidity.

**REFERENCES**


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