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Research Paper

Treatment of Adult Onset Multifocal Single System Langerhans Cell Histiocytosis Using Single Agent Induction Chemotherapy Followed By Maintenance Oral Etoposide and External Beam Radiotherapy: A Case Report

Medical Science

KEYWORDS : Langerhans Cell Histiocytosis, Adult, Etoposide

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ABSTRACT

Adult onset Langerhans cell Histiocytosis is a rare disease that has a prolonged and relatively benign course compared to its more common juvenile-onset variant. Lack of consensus in limited multi-centric trials and treatment guidelines, particularly in the multisystem and multifocal single system variants need further assessment. Choosing a disease limiting chemotherapeutic drug regimen with minimal adverse effects is therefore, the need of the hour. Our endeavour was to replicate the success of monotherapy with Etoposide in children as seen in previously published case reports, in a patient with adult onset multifocal osseous Langerhans Cell Histiocytosis.

INTRODUCTION

Chronic Langerhans cell histiocytosis (LCH) in the adult is a rare, poorly understood and difficult-to-treat disease, with no established treatment protocols due to paucity of clinical trials. The treatment options in the case of multifocal disease include expectant approach, chemotherapy, and radiotherapyor a combination of these modalities. Commonly used chemotherapeutic regimens include vindesine and prednisone (VP) and cyclophosphamide, etoposide, vindesine, and prednisone (CEVP) as first-line treatment for multifocal single system (SS-m) Adult Langerhans cell histiocytosis (LCH). These showed similar efficacies though were associated with high disease recurrence and the need for second-line therapy. [1] Etoposide has been used for the treatment of paediatric LCH. However, experience with etoposide in the rare, disseminated adult LCH is sporadic and limited to single cases treated by high-dose or combination schedules. [2-6]Disseminated adult LCH in contrast to the juvenile type, has a more benign character and slow progression. This in turn favours prolonged treatment with minimal adverse effects, until a curative treatment schedule is established. The clinical responses to low-dose oral etoposide in previously published case reports encouraged us to try the same, well-tolerated monotherapy in a case of multifocal osseous LCH in a middle-aged adult with multifocal bone disease without visceral involvement.

CASE REPORT

A 44 year old male smoker presented to our radiotherapy department with progressively worsening tooth ache in the left lower molar region & intermittent low back pain radiating to the right sacroiliac joint for two years. Over the counter non-opioids provided minimal relief.

There was no history of trauma, night sweats, low grade fever or significant past medical/surgical/medication history.

On examination, the patient had a good performance status of ECOG-0, no pallor, icterus, clubbing, pedal oedema or any skin lesions. There was no evidence of any palpable generalised lymphadenopathy. Oral hygiene was poor. Multiple teeth were missing.

Full blood cell count with differential, serum electrolytes, kidney &liver function tests, alkaline phosphatase, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were all found to be within normal limits.

On imaging, the dental panoramic radiograph **(figure 1A)** revealed an area of bony destruction in the left mandible beneath the apical region, an impacted left lower third molar and bony resorption around the first left lower molar.

Computed Tomography (CT) scan of the face and neck region **(figure 2)** revealed a small soft tissue lesion in the floor of the left maxillary sinus causing bony destruction and extension into periantral fat, another soft tissue lesion was noted abutting the mandible in the midline, causing erosion of the buccal cortex. Also of significance was an expansile soft tissue lesion in the body of the mandible in the left para median location causing erosion of the outer and inner mandibular cortex. There were multiple bilaterally enlarged level I and II cervical lymph nodes, the largest of which measured 18 X13 mm.

Technetium Bone scintigraphy **(figure 3)** revealed increased radiotracer uptake over the right supraorbital arch, Right sacro-iliac joint and adjoining iliac bone, as well as the left pubic bone. Chest X-Ray suggested patchy apical fibrosis in the Right upper lobe possibly suggestive of an old Koch's lesion. Ultrasound of the abdomen was normal.

Incisional biopsy from the alveolar lesions was done, histopathology of which revealed Langerhans cell histiocytosis. Immunohistochemistry of the tissue block was found to be positive for CD-1a and S-100, authenticating the diagnosis.

Due to the multifocal involvement, it was decided to start induction chemotherapy with Injection Etoposide (100 mg) intravenously for three days, each cycle lasting 21 days. He received 4 such cycles of monotherapy without undue side effects. Blood parameters were monitored prior to each cycle and found to be within normal limits. Comparative CT scan of the face and neck region taken post chemotherapy showed a decrease in size of the soft tissue lesion both in left paramedian location and the lesion causing the erosion of the mandibular cortex, with no new fresh lesions.

In addition, he received External Beam Radiotherapy (EBRT) of 20 Gy in 10 fractions (2 Gy/ fraction) over two weeks to the lower mandibular region. No acute or chronic toxicities of radiation therapy have been observed thus far.

Review dental panoramic radiograph revealed a cystic area with sharp margins in the left mandible **(figure 1B)**. The patient was asymptomatic and the pain in the left lower molar region as well as the low back pain had completely subsided. Owing to the persistent residual lytic lesions, the patient was started on oral maintenance monotherapy with

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Etoposide. He was given tablet Etoposide (50mg/m^2) for 21 days. The cycle was repeated every 28 days for 6 cycles.

The patient has been on regular follow-up for the past 6 months, and barring mild intermittent pain the left upper teeth for the past 4 months, his overall condition has improved clinically. On imaging **(figure 1C)**, the lytic lesion in the left hemi mandibular body seen at the para median location has significantly decreased in size with new bone formation. There are a few sub centimetric lymph nodes in the level I and II cervical region. We plan to keep the patient under close observation & regular follow-up with a complete skeletal survey with Technetium Bone Scintigraphy.

DISCUSSION

The working group of the Histiocyte Society has divided histiocytic disorders into 3 groups: (1) dendritic cell histiocytosis, (2) macrophage-related disorders, and (3) malignant histiocytosis [7] with LCH being categorised under group 1.

It affects mainly children with a peak incidence from 1 to 5 years with an incidence of 1/20,000 per year with a male predilection (male-to-female ratio of 2:1) [8]. Adult LCH is rarer and its reported incidence is around one to two cases per million people per year [9].

The bone lesion can be solitary or multiple, they are located mainly in the flat bones most commonly in the skull (51%), the jaw (30%) causing loss of teeth. Rarely does it affect tubular bones (17%), pelvis (13%), and ribs (6%) [10]

The Writing Group of the Histiocyte Society classified LCH according to the number and type of organs involved, defining single system and multisystem disease, low risk patients (with liver, spleen and bone marrow involvement) and high-risk patients (with skin, bone, lung, lymph nodes, gastrointestinal tract, pituitary gland, central nervous system involvement) [11]

Radiological diagnostic examination should include entire skeletal X-ray, a chest X-ray, and an ultrasound of the abdomen. In osseous LCH, entire skeletal X-ray shows typically single or multiple osteolytic lesions round or oval-shaped with well-defined contours [12]. Bone involvement often results in a cortical blowing and a periosteal reaction or endosteal scalloping, resulting in the "budding appearance" on CT or MRI. [13]

Systemic chemotherapy is indicated for multisystem & multifocal single system disease, with low-to-moderate doses of methotrexate, etoposide, prednisone, and vinblastine being the commonly used cytotoxic agents.

However, there are currently no established treatment guidelines for adult onset LCH and the chemotherapeutic agents that have been used in the adult population are those that have been proven to be efficacious in multiple trials conducted in the paediatric age group, possibly due to poor sample size and lack of multi-centric trials.

Most series emphasize the effectiveness of radiation therapy alone or in combination with corticosteroids in unifocal or multifocal osseous single system disease with good results. [14] The dose recommendation for radiotherapy is still controversial. There is a wide dose range, though 10-20 Gy in conventional fractionation is recommended in adults.

The results presented herein suggest that oral etoposide does not have a complete curative effect, but a disease-controlling effect as was demonstrated for 10 months (5 during therapy and 5 thereafter).

CONCLUSION

Owing to the low incidence of LCH adults and the lack of published data on the pathogenesis, categorization and treatment guidelines of adult onset LCH, patients must be enrolled on multi-national clinical trials, whenever possible, to tailor chemotherapy while minimizing toxicity given the relatively long survival of patients even with multi system and multifocal single system LCH. This would lead to better understanding of the disease and in turn better long term outcomes.

FIGURES

Figure 1 (from top to bottom, A-C)

1. Dental panoramic radiographs showing an area of bony destruction in the left mandible beneath the apical region with bony resorption around the first left lower molar.
2. a cystic area with sharp margins in the left mandible
3. Significantly decreased in size with new bone formation.

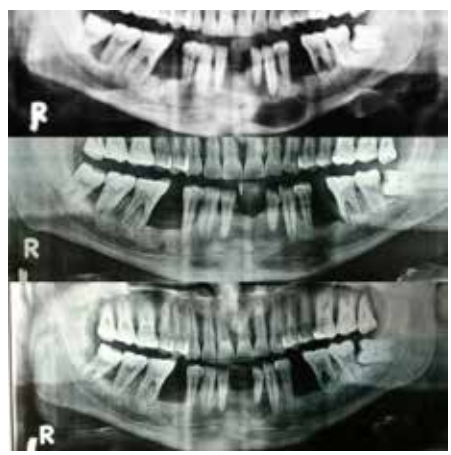


Figure 2
Computed tomography (3D reconstruction) showing an expansile soft tissue lesion in the body of the mandible in the left para median location causing erosion of the outer and inner mandibular cortex.

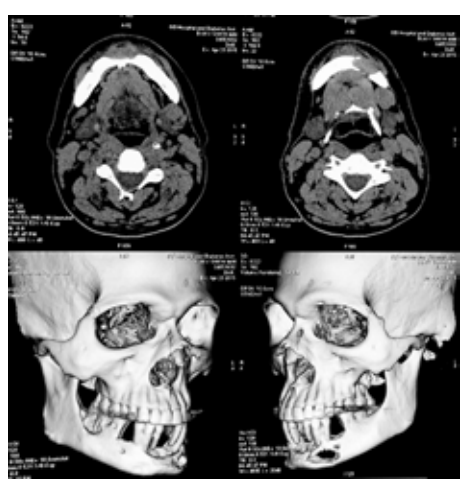
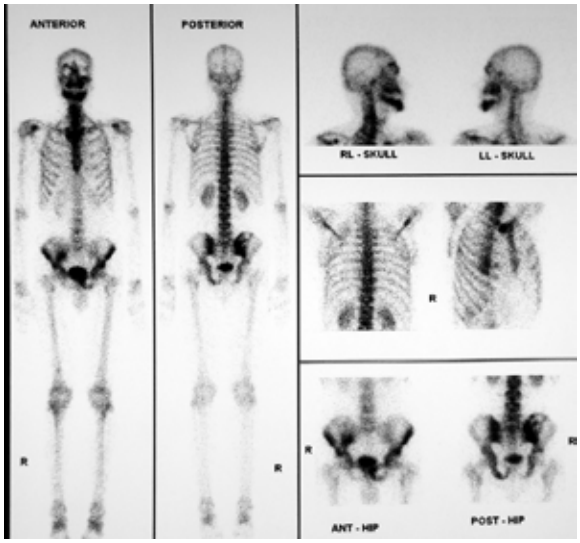


Figure 3
Technetium Bone scintigraphy showing increased uptake over the right supraorbital arch, Right sacro-iliac joint and adjoining iliac bone.



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