CASE REPORT

Into the wild world of eosinophilic granuloma

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SUMMARY

Langerhans cell histiocytosis (LCH) is a group of relatively rare disease processes of reticuloendothelial system with an abnormal proliferation of Langerhans cells or their precursors. A wide spectrum of treatment modalities is available for LCH which includes surgery, curettage, steroids, radiation, various chemotherapy regimens, either in combination or alone have so far been adopted. There are several case reports of eosinophilic granuloma but for recurrent cases very few have discussed on treatment of LCH in adults. We report a case of a 21-year-old man presented with eosinophilic granuloma with recurrence of the lesions after 6 years of the initial treatment. Patient was treated with combination chemotherapy with three weekly CHOP regimen and the patient is disease free after 6 months of follow-up. Contrary to other reports, this case demonstrates that a good response with standard therapy is possible.

CASE PRESENTATION

A 21-year-old man presented with swelling and intense pain affecting the left lower gums. It had been present for 3 months and with a painful growth. Initially it started as swelling in the left lower gums with dull ache. Pain was mild in intensity and only relieved after taking low-dose prednisolone with non-steroidal anti-inflammatory drugs (NSAIDs). There was history of bleeding from the gums and the ulcerated lesion. Patient was a non-smoker and a non-alcoholic, no other comorbidities were noted. Patient left on follow-up and reported after 6 years of the initial presentation and presented with three new lesions present over the hard palate and lower alveolus. The first lesion was present on the right side, 1.5×1.5 cm in size and opposite to first and second molar tooth, the second lesion was present on the left side, 1.0×0.5 cm in size and opposite to the first molar tooth and third lesion was present on the right side, 2.0×1.5 cm in size, over lower alveolus.

BACKGROUND

Historically, Lichtenstein and Jaffe in 1940 first described eosinophilic granuloma. Langerhans cell histiocytosis (LCH) is a rare disease of unknown pathogenesis, characterised by the intense and abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells). It can present both local and systemic manifestations involving bone, skin and mucosal tissue and internal organs. Subsequently, Lichtenstein proposed that eosinophilic granuloma (localised chronic form), Hand-Schuller-Christian (disseminated chronic form) and Letterer-Siwe disease (subacute or acute disseminated form) represent manifestations of a single entity, termed as Histiocytosis X. In 1987, the Writing Group endorsed the use of the term 'LCH' for all these forms. Langerhans cells are part of the mononuclear phagocytic system. Despite ambivalence, increasing evidence suggests the role of immune abnormality resulting in abnormal proliferation of histiocytes.¹

INVESTIGATIONS

Orthopantomogram of the patient was normal with no obvious bony lesion (figure 1). The patient was investigated for histoplasmosis but non-evident on histopathological examination. Subsequently incisional biopsy was taken from the first molar of the left lower lingual gingiva. The histopathological findings revealed eosinophilic granuloma (figure 2). 99mTc-MDP Radio-Isotope bone scan was not suggestive of any osteoblastic pathology in the left mandible or elsewhere in the skeletal system (figure 3A,B). Subsequent to these investigations, this patient was labelled as a case of Stage IIIB, soft tissue only disseminated form of LCH.

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Figure 1 Pretreatment orthopantomogram—normal study.

Figure 2 Photomicrograph H&E stain; magnification×400 revealed Langerhans cell histiocytosis.

Figure 3 (A)
Pretreatment-99mTc-MDP
Radio-Isotope whole body bone scan.
(B) Pretreatment-99mTc-MDP
Radio-Isotope bone scan.

DIFFERENTIAL DIAGNOSIS

Whenever LCH is suspected all hematological investigations should be carried out. Surgical exploration and biopsy are essential in diagnosis. Histopathological diagnosis may be established through histochemical analysis or electron microscopy. Histochemical analysis may show positive cells for HLA-DR

glycoprotein, S-100 protein, peanut agglutinin and CD1a thymocyte glycoprotein (Leu6), Langerin (CD207), CD68 coexpression may be found in CD1a and Langerin-positive cells. Owing to the high heterogenous nature of this rare group sometimes lack of nuclear atypia and atypical mitoses is also observed. The differential diagnosis of LCH of bone with a multifocal pattern in adults is

Figure 4 (A) Fluoro-deoxyglucose positron emission tomography (FDG PET) scan of head and neck area after the completion of treatment showing normal study. (B) FDG PET whole body scan after the completion of treatment showing normal study.

osteomyelitis, ewings sarcoma, hyperparathyroidism, multiple odontogenic keratocyst, multilocular cyst, leukaemia, lymphoma and with unifocal pattern is osteolytic metastasis, multiple myeloma, myxoma, ameloblastoma and osteogenic sarcoma. The differential diagnosis for the oral mucosal lesion includes advanced periodontal disease, periapical abscess and sarcoidosis. The gold

standard of diagnosis has been the identification of ultrastructural Birbeck or Langerhans cell granules on electron microscopy, which possess tennis-racket morphology with well-defined round or oval cytoplasm, oval nuclei with transverse striations and are thought to be specific markers of Langerhans cells, as none of the other tissue or cell markers is unique to LCH.²

TREATMENT

The patient was started on combination chemotherapy with a three weekly CHOP regimen (cyclophosphamide 750 mg/m² intravenously day 1, doxorubicin 50 mg/m² intravenously day 1, vincristine 1.4 mg/m² intravenously day 1 and prednisolone 100 mg orally day 1–5).

OUTCOME AND FOLLOW-UP

The lesions disappeared completely after the third cycle of CHOP regimen and it was decided to give a total of eight cycles of CHOP-based chemotherapy. The patient is disease free after 1 year of follow-up as evident from the whole body positron emission tomography scan also (figure 4A,B).

DISCUSSION

LCH is a rare disease with a wide variety of clinical presentations and course.³ Lichtenstein gave the term histiocytosis in 1953 to include three clinical varieties including eosinophilic granuloma, Hand-Schüller-Christian and Letterer-Siwe disease. In 1987, the Writing Group endorsed the use of the term 'LCH' for this clinically heterogeneous group to designate the various clinicopathological conditions previously known as 'Hand-Schuller-Christian disease', 'Abt-Letterer-Siwe disease', 'Hashimoto-Pritzker disease' and 'eosinophilic granuloma of bone'. The relative incidence of LCH is not well known, due principally to the heterogeneous clinical expression, but is estimated at approximately 2–5 cases per million inhabitants per year, being more frequent between the first and third decades of life, although it may affect any age group. Eighty per cent of cases occur in Caucasians, with predominance in men. Oral manifestations may be the first sign of LCH, and on some occasions the oral cavity may be the only area affected. The incidence of oral lesions in LCH is 77%. Oral lesions can be classified further to bone, mucosal and periodontal lesion.⁴ Eden,⁵ in 1998, staged LCH as: Stage I, single lytic bone lesion; Stage II multiple lytic bone lesions (both formerly termed as eosinophilic granulomata); Stage IIIA, bone plus soft tissue lesions, often associated with diabetes insipidus (pituitary involvement) or exophthalmos (previously termed Hand-Schuller-Christian triad); Stage IIIB, soft tissue only disseminated form (previously termed Letterer-Siwe disease).

Currently, with respect to LCH, response is defined as a measurable resolution of symptoms and signs and the prevention of permanent consequences of the disease. To some extent, treatment reflected early views on disease pathogenesis, that is, granulomatous, inflammatory or infectious.¹ Consequently children with LCH were treated with antibiotics, with anti-inflammatory agents including steroids, with radiation therapy and over the last 20–30 years, with cytotoxic chemotherapy. Lack of understanding of the pathogenesis of LCH and the heterogeneity of clinical presentation not only impeded the adoption of a generally accepted clinical and histopathological staging and classification system, but also the adoption of a rational treatment policy. Our case, which was pathologically labelled as LCH, underwent some other important investigations such as orthopantomogram to rule out any obvious bony lesion and 99mTc-MDP Radio-Isotope bone scan for any osteoblastic pathology in the affected area or elsewhere in the skeletal system. Based on all these investigations, the present case was diagnosed as a Stage IIIB, soft tissue only disseminated form of LCH, which initially responded very well to low-dose steroid and NSAIDs but later the disease progressed and decided for the consideration of combination chemotherapy. Major obstacles were the changing belief that LCH is a reactive rather than a malignant process and the inability to identify

prognostic factors which could predict outcome. This explains why treatment of a disease which may be acute, subacute or chronic as well as progressive, stable or sometimes spontaneously regressing, becomes controversial. Two major approaches exist; conservative approach using minimal therapy and intensive chemotherapy treatment plan.^{1–6} Different protocols have been suggested in literature for treating eosinophilic granuloma. For patients with more extensive disease, there is general agreement, based on many published studies of substance, that systemic chemotherapy will be beneficial. The exact type of chemotherapy that is best has not been completely worked out, although several different drugs and combinations have been shown to give excellent results with relatively minimal side effects. Chemotherapeutic agents include steroids (eg, prednisone), vinblastine, vincristine, etoposide, 6-mercaptopurine and methotrexate.⁷ Combination chemotherapy has proved better results and in view of the same we have opted for combination chemotherapy with CHOP. Further, due to its highly heterogeneous nature an evidence-based treatment protocol should be established through a series of randomised therapeutic trials and international collaboration. Recent trials show response towards many chemotherapeutic combinations which includes cytosine arabinoside (ARA-C) and cladribine.^{8–9} Research is on-going regarding the optimal chemotherapeutic regimen and new therapeutic regimens can be added in case of suboptimal response and recurrence cases already on treatment.

Learning points

- ▶ Patients need to be managed in the context of interdisciplinary approach to establish an accurate diagnosis and adequate treatment.
- ▶ A longer follow-up is mandatory to avoid the chances of possible expansion of disease in multiple organs and involvement of bony site or probable recurrence in later stage of life.
- ▶ Optimal combination chemotherapeutic regimen should be considered for improved prognosis.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Atri R, Dhankhar R, Dhull AK, et al. Alveolar Langerhans cell histiocytosis—a case report. *J Oral Health Commun Dent* 2008;2:16–18.
- 2 Jaffe R. Diagnostic pediatric hematology. *Clin Lab Med* 1999;19. <http://www.histiocytosisociety.org/document.doc?id=47>
- 3 Pan Z, Sharma S, Sharma P. Primary Langerhans cell histiocytosis of the vulva: report of a case and brief review of the literature. *Indian J Pathol Microbiol* 2009;52:65–8.
- 4 Madrigal-Martínez-Pereda C, Guerrero-Rodríguez V, Guisado-Moya B, et al. Langerhans cell histiocytosis: literature review and descriptive analysis of oral manifestations. *Med Oral Patol Oral Cir Bucal* 2009;14:E222–8.
- 5 Eden OB. Oncology and terminal care. In: Campbell AGM, McIntosh N, eds. *Forfar and ArNeil's: textbook of pediatrics*. New York: Churchill Livingstone, 1998:884–934.
- 6 Stephan L, Helmut G. Treatment of Langerhans cell histiocytosis—evolution and current approaches. *Br J Cancer* 1994;70:541–46.
- 7 Abrahão AC, Cabral MG, Noce Dos Santos CW, et al. Polyostotic eosinophilic granuloma of the jaws treated by chemotherapy—a case report. *Minerva Stomatol* 2007;56:405–9.
- 8 Cantu MA, Lupo PJ, Bilgi M, et al. Optimal therapy for adults with langerhans cell histiocytosis bone lesions. *PLoS ONE* 2012;7:e43257.
- 9 Adam Z, Szturp P, Duraš J, et al. Treatment of Langerhans cells histiocytosis by cladribin reached long-term complete remission in 9 out of 10 adult patients. *Klin Onkol* 2012;25:255–61.

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