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Case Report

Langerhans Cell Histiocytosis with Good Response to Low-Dose Imatinib: Case Report and Literature Review

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Keywords
Histiocytic cell neoplasms · Dendritic cell neoplasms · Histiocytosis · Tyrosine kinase inhibitors · Positron emission tomography scan

Abstract
Langerhans cell histiocytosis (LCH) is a rare neoplastic disease characterized by infiltration of histiocytes and dendritic cells into body organs. While treatment is better established in pediatrics, there is still no consensus on therapy in the adult population. Imatinib has shown promising results in some case reports and a small clinical trial. We present here a fifty-nine-year-old patient with LCH in the lung, liver, and bone who responded well to an imatinib dose of 100 mg daily. Her symptoms improved within 3 months of treatment, and subsequent positron emission tomography-computed tomography (PET/CT) showed resolution of 18F-fluorodeoxyglucose (FDG)-avid lesions.

Introduction

Histiocytosis is a spectrum of diseases characterized by the infiltration and accumulation of dendritic cells, macrophages, or monocyte-derived cells in various body tissues and organs. These cells are related to different lineages of accessory antigen-presenting cells (dendritic cells) that play a role in phagocytosis, processing, and presentation of antigens to lymphoid cells [1]. In 2016, the International Histiocyte Society proposed a revised classification that

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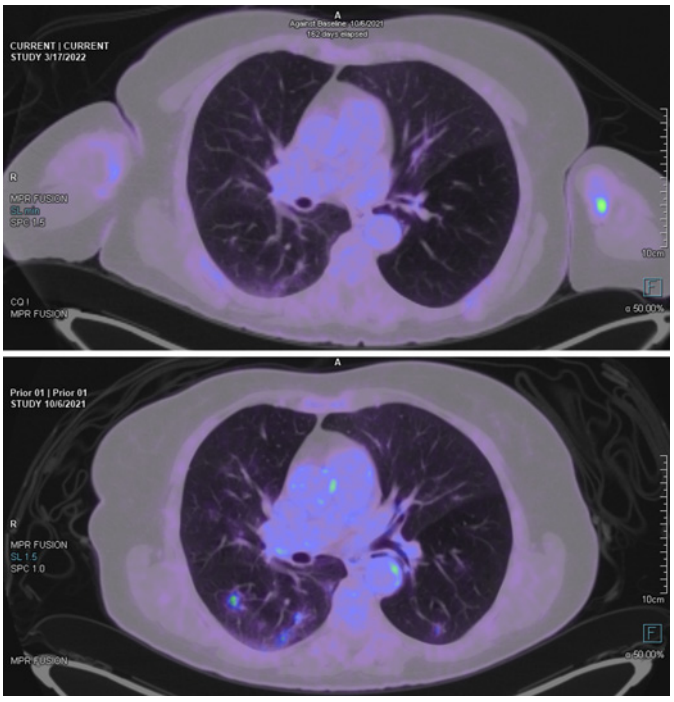

Fig. 1. PET scan of the lung before (down) and after (up) treatment showed near complete resolution of multiple lung FDG-avid nodules.

includes five major groups: Langerhans-related, cutaneous and mucocutaneous, malignant, Rosai-Dorfman disease, and hemophagocytic lymphohistiocytosis and macrophage activation syndrome [2].

Histiocytic tumors are among the rarest tumors of lymphoid tissue and probably account for less than one percent of lymph node and soft tissue tumors. The annual incidence of Langerhans cell histiocytosis (LCH) is approximately 5 per million, with most cases occurring in children [3]. Langerhans cells are specialized dendritic cells in the skin and mucous membranes. LCH is a neoplastic disease of dendritic cells characterized by polymorphic cellular infiltration and damage to single or multiple organs and tissues. Although LCH dendritic cells express similar markers to Langerhans cells of the skin, they are thought to be derived from a different myeloid dendritic cell precursor. Histologically, LCH lesions contain Langerhans cells against a background of a mixture of eosinophils, neutrophils, and lymphocytes [4].

Somatic mutations have been identified in over 70% of LCH patients, most commonly the BRAF V600E mutation. Even in patients without identified mutations, virtually all tumors exhibit excessive MEK and ERK phosphorylation, suggesting that extracellular signal-regulated kinases control LCH pathogenesis [5]. Other less common mutations involve platelet-derived growth factor receptors (PDGF-R) and a KIT (CD117) kinase [6].

LCH may affect a single site or multiple sites in one organ system or occur simultaneously or sequentially in multiple organ systems. Symptoms include progressive bone pain or swelling, skin rash, ear discharge, dyspnea, cough, and pneumothorax, depending on the site of involvement [7]. Up to 30% of patients may develop diabetes insipidus, which could be due to intracranial extension of craniofacial bone lesions or infiltration of the pituitary stalk [8].

Treatment with imatinib is not a standard of care, but some case reports and a small clinical trial showed good results with minimal side effects [9]. Here, we report a case of multisystem LCH that was successfully treated with imatinib within 3 months without

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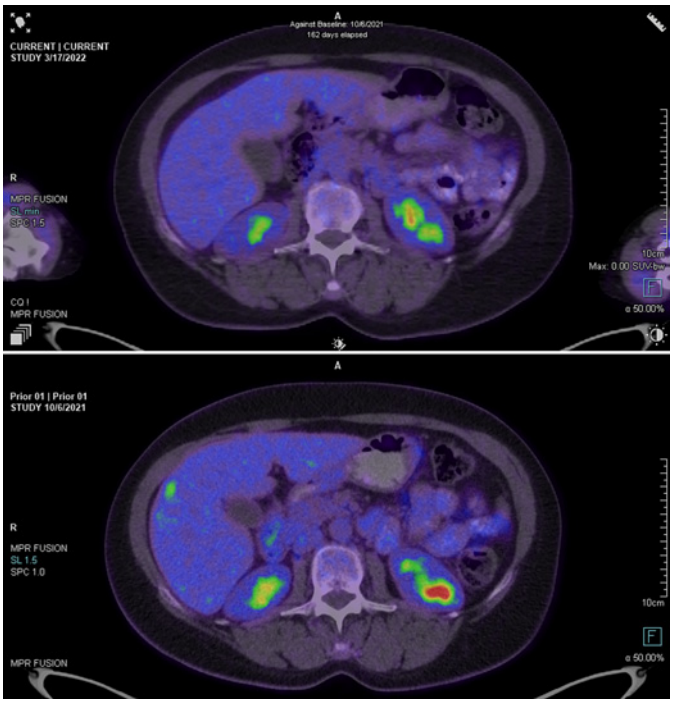

Fig. 2. PET scan of the liver before (down) and after (up) treatment showing resolution of focal liver uptake.

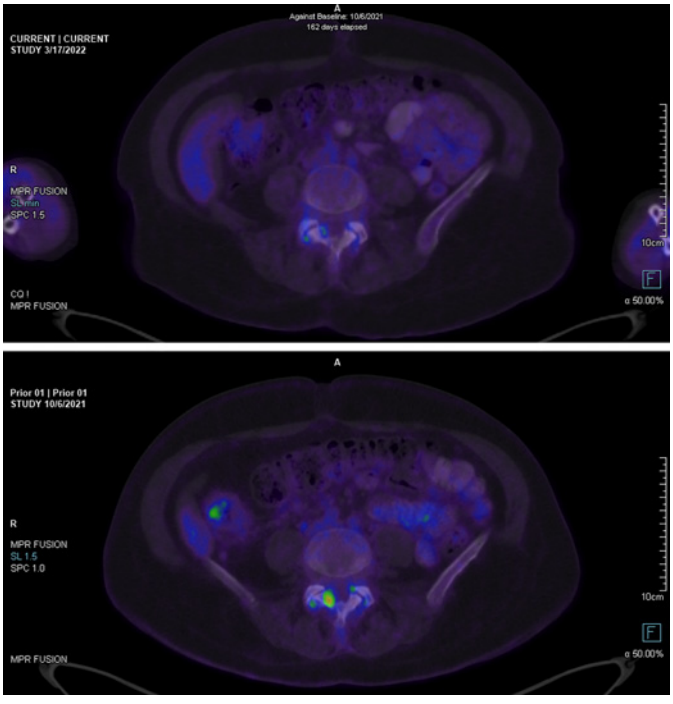

Fig. 3. PET scan of the vertebral bone (down) and after (up) treatment showing near complete resolution of the L4 bone lesion.

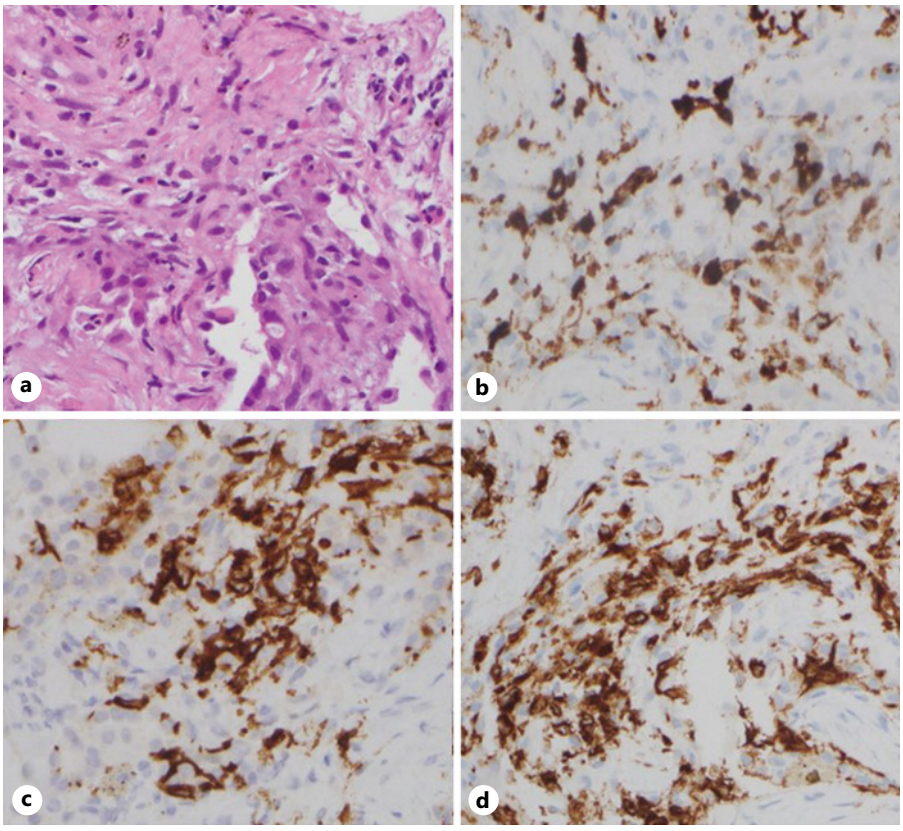

Fig. 4. Langerhans cell histiocytes infiltrate the lung parenchyma with occasional eosinophils in the background (**a**), *CD68* (**b**), *CD1a* (**c**), and Langerin (**d**) (hematoxylin-eosin, original magnification ×400 [**a**] and immunohistochemical stains, original magnification ×400 [**b–d**]).

significant side effects, as evidenced by clinical improvement and repeated PET scans. Compared to other options, imatinib is safer and more tolerable, but further studies are needed to demonstrate its efficacy. The CARE checklist was completed by the authors for this case report and is included as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531230).

Case Presentation

Fifty-nine-year-old woman with a history of hypertension and a 40-year smoking history presented with persistent cough and shortness of breath for 3 months; there was no fever, weight loss, or rash. On examination, there were no significant findings, lymphadenopathy, or palpable organomegaly. Other than a mildly elevated LDH, basic laboratory tests revealed no significant abnormalities. CT scan of the chest revealed bilateral pulmonary nodules that were fluorodeoxyglucose (FDG)-avid at PET (Fig. 1). PET scan also showed FDG-avid, solitary liver lesion (Fig. 2), and multiple bone lesions (Fig. 3). Histopathological examination of the pulmonary nodule (Fig. 4) revealed features consistent with Langerhans histiocytosis. Bone marrow examination revealed no evidence of bone marrow involvement.

The patient was offered systemic chemotherapy with methotrexate, vinblastine, and prednisolone; the pros and cons were explained, but she refused any chemotherapy, so she was started on imatinib 100 mg daily with firm advice to stop smoking. Four months later, she

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Table 1. Case reports describing the use of imatinib in 6 LCH patients

Case number	Author, year	Type of study	Age/ sex	Disease involvement sites	Molecular mutation	Previous treatment	Imatinib dose	Treatment duration	Significant toxicity	Response assessment modality	Outcome
1A	Janku et al. [10] (2010)	Case report	31/ female	Bone, lung, and brain	There were no KIT mutations. PDGFRA mutation analysis was not successful because of an insufficient amount of DNA	Whole-brain external beam radiation and then commenced on interferon alfa-2b	400 mg/d then later increased to 600 mg/d	11 months	Not mentioned	Clinically and PET scan	Favorable response
1B	Janku et al. [10] (2010)	Case report	55/ male	Skin and lung	There was no KIT or PDGFRA mutations	None	400 mg/d	6 months	Not mentioned	Clinically and CT scan	Favorable response
2	Montella et al. [15] (2004)	Case report	37/ female	Brain	Strongly positive for PDGF receptor beta and were negative for KIT mutation	Whole-brain radiotherapy plus treatment with dexamethasone, mannitol, and phenobarbital	100 mg/d then increased to 400 mg daily	18 months	Not mentioned	Clinically and MRI	Favorable response
3A	Wagner et al. [17] (2009)	Case report	21/ male	Bone, lung, and skin	Not mentioned	None	600 mg/d	3 months	Not mentioned	Clinically	Disease progression
3B	Wagner et al. [17] (2009)	Case report	84/ male	Skin	Not mentioned	None	600 mg/d	Not mentioned	Well tolerated	Clinically	Disease progression
4	Baumann et al. [13] (2011)	Case report	20/ male	Brain and bone	Not mentioned	Sorafenib	Not mentioned	2 months	Well tolerated	Clinically and MRI	Disease progression

MRI, magnetic resonance imaging.

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Table 2. Adapted from TETimaX trial done by Montella et al. [15] who assessed the role of imatinib in LCH treatment

Patient number	Age	Sex	Disease involvement sites	Previous treatment	Best outcome and timeframe	Follow-up after imatinib
1	25	Male	Lung and bone	Vinblastine + prednisone	Complete remission (10 years)	12 years + 1 month
2	46	Female	Lung	Vinblastine + prednisone	partial remission (10 years)	11 years + 6 months
3	41	Female	Lung, brain, and bone	Vinblastine + prednisone, cladrabine, indomethacin	Brain and bone complete remission, lung partial remission (9 years)	8 years + 6 months
4	60	Male	Bone and retroperitoneal fibrosis	Vinblastine + prednisone	Stable disease	9 years
5	36	Male	Bone	Vinblastine + prednisone	Complete remission	12 years + 7 months

has reduced smoking to five to ten cigarettes per day, her symptoms have decreased, and a repeat PET/CT scan showed a nearly complete resolution of multiple lung lesions (Fig. 1), resolution of focal liver uptake (Fig. 2), and the L4 bone lesion (Fig. 3). She completed 1 year of treatment, and no significant side effects or recurrence of her symptoms were observed. The patient was given the choice of discontinuing the treatment and close monitoring or continuing the treatment until disease progression or relapse. She chose to continue the treatment.

Discussion

Treatment of LCH depends on the severity and activity of the disease. Single-organ systems (SS-LCH) have a favorable prognosis and usually require minimal or no treatment [10]. Multiple systems (MS-LCH) and SS-LCH with multifocal involvement or involvement of critical anatomic sites are treated with systemic therapy, including vinblastine, methotrexate, and prednisone. However, there is no consensus on the optimal treatment for adult patients [11]. Response is best assessed with positron emission tomography (PET). Nevertheless, computed tomography (CT), magnetic resonance imaging, or clinical assessment are used when PET is not available or is not the best option (e.g., in brain lesions) [12].

Treatment with imatinib is not a standard of care, but some case reports and a small clinical trial showed good results with minimal side effects. Imatinib is designed to block the ATP-binding site in the BCR/APL protein, and it is also an inhibitor of PDGF-R and a KIT (CD117) kinase found in some LCH cases [13, 14]. Reviewing the literature, we found 4 case reports describing the use of imatinib in 6 LCH patients (Table 1), and one clinical trial evaluated the efficacy of imatinib in LCH; the TETimaX trial conducted by Montella et al. [15] investigated the role of imatinib in the treatment of LCH, administered at a daily dose of 400 mg for 1 year after discontinuation of all previous treatments. Five patients were enrolled in the clinical portion of the study, and all achieved long-lasting disease control [16] (Table 2).

Imatinib was used as first-line therapy in three cases and as second-line therapy in the other eight cases. The dose was 400 mg in all published cases, except in one case where the dose was not mentioned and in another case where it was started at 100 mg and then increased

to 400 mg. Of the 11 published cases, eight had a good response ranging from stable disease to complete remission, and three had disease progression with imatinib. Imatinib was well tolerated in all cases, and no significant toxicity was observed. The exact underline mechanism for the therapeutic effect of imatinib in some LCH patients is not yet well understood. However, there are some hypotheses, including inhibition of PDGFRB, which is frequently expressed in LCH, and differentiation of CD34 progenitor cells into dendritic cells [5].

Conclusion

LCH is a rare disorder with no clear guidelines for its treatment in adult patients. Low-dose imatinib may be a safe and effective option for some patients, but further studies are needed to explore the underlying mechanism of action and demonstrate its efficacy.

Acknowledgment

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Statement of Ethics

This case was approved by the Hamad Medical Corporation's Medical Research Centre, under approval number MRC-04-23-054. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

M.A. was involved in the literature review, writing, editing, and final approval. D.M. was involved in the literature review and final approval. Z.L. was involved in reviewing the radiological figures. H.A.S. was involved in reviewing the histopathological figures. A.A. gave the final approval. M.A.Y. was involved in the literature review, editing, and final approval.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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