Everolimus in Erdheim–Chester disease

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A 43-year-old man presented with bony pains, repeated pathological fractures with overlying skin ulcerations, and forearm and chest wall swellings. Investigations led to the diagnosis of Erdheim–Chester disease. Treatment with low-dose prednisolone, oral everolimus, and zoledronic acid was started, with a marked improvement in his condition.

Keywords:
Erdheim–Chester disease, everolimus, lipid-storing histiocytosis, pathological fractures, Touton giant cells

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Case report

A 43-year-old male patient with chronic industrial exposure to car exhaust had a 9-year history of repeated pathological fractures of the left radius and the left tibia and subsequent ulcerations of the skin of the left forearm, causing a large swollen raw area, followed by two swellings in the anterior chest wall. Computed tomography (CT)-guided biopsy from the left radius was consistent with Erdheim–Chester disease (ECD). Different lines of treatment were attempted including NSAIDs, calcitonin, zoledronic acid (Aclasta, Novartis, Basel, Switzerland) 5 mg, oral prednisolone, methotrexate, and a single dose of radiotherapy, with limited improvement.

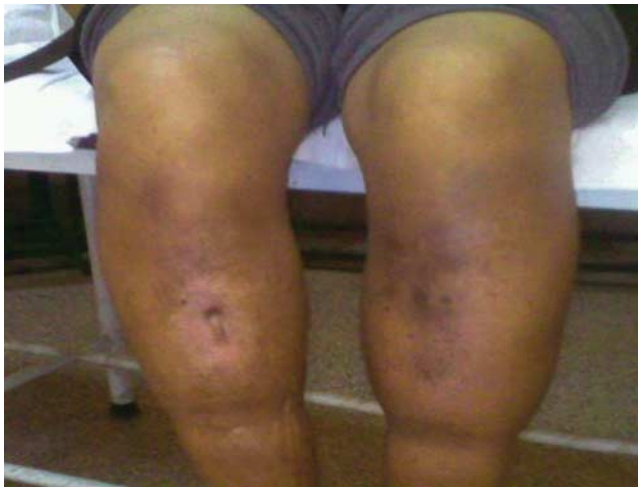
He presented to us for re-evaluation. His initial examination indicated a regular radial pulse, 80/min, with intact peripheral pulsations, blood pressure was 120/70 mmHg, the left forearm was swollen with multiple ulcers and raw areas, the left leg showed an area of skin pigmentation, scar, and swelling at the site of radiotherapy, with minimal left knee effusion (Fig. 1). Two ovoid, hard, and immobile swellings were present on the anterior chest wall and hepatosplenomegaly.

His laboratory investigations showed no abnormalities apart from mild polymorphonuclear leukocytosis, anemia, and elevated erythrocyte sedimentation rate and C-reactive protein. CT left forearm with intravenous contrast was performed and showed a large soft tissue mass destroying distal two-third of the radius and upper one-third of the ulna just distal to humeroulnar articulation (Fig. 2). Arterial duplex left upper limb and plethysmography on the left hand showed normal digital blood flow. A confirmatory CT-guided biopsy from one of the anterior chest wall swellings (Fig. 3) showed lipid-storing histiocytosis (foam cells) and pathognomonic Touton giant cells besides multinucleated giant cells that were consistent with ECD (Fig. 4). Treatment with symptomatic analgesia (diclofenac), oral prednisolone 10 mg, three-weekly intravenous zoledronic acid (Zometa, Novartis) 4 mg, and oral everolimus 5 mg/day was started, with a marked improvement in his condition.

Discussion

ECD is a rare non-Langerhans-cell histiocytosis characterized by tissue infiltration with foamy histiocytes. The disease almost invariably affects bones, causing the nearly pathognomonic osteosclerosis of the limbs [1]. Bone pain is the most frequent symptom, mainly affecting the lower limbs, knees, and ankles [2]. The bony lesions in ECD are typically symmetric and sclerotic and involve the long bones in the region of the metadiaphyses [3]. However, Pertuiset *et al*. [4] reported a new case of ECD documented by two bone biopsies in different sites with features of osteolysis and evidence of cortical rupture. Some patients also showed extraskeletal manifestations,

Figure 1



Leg showing area of skin pigmentation, scar, and swelling at the site of radiotherapy.

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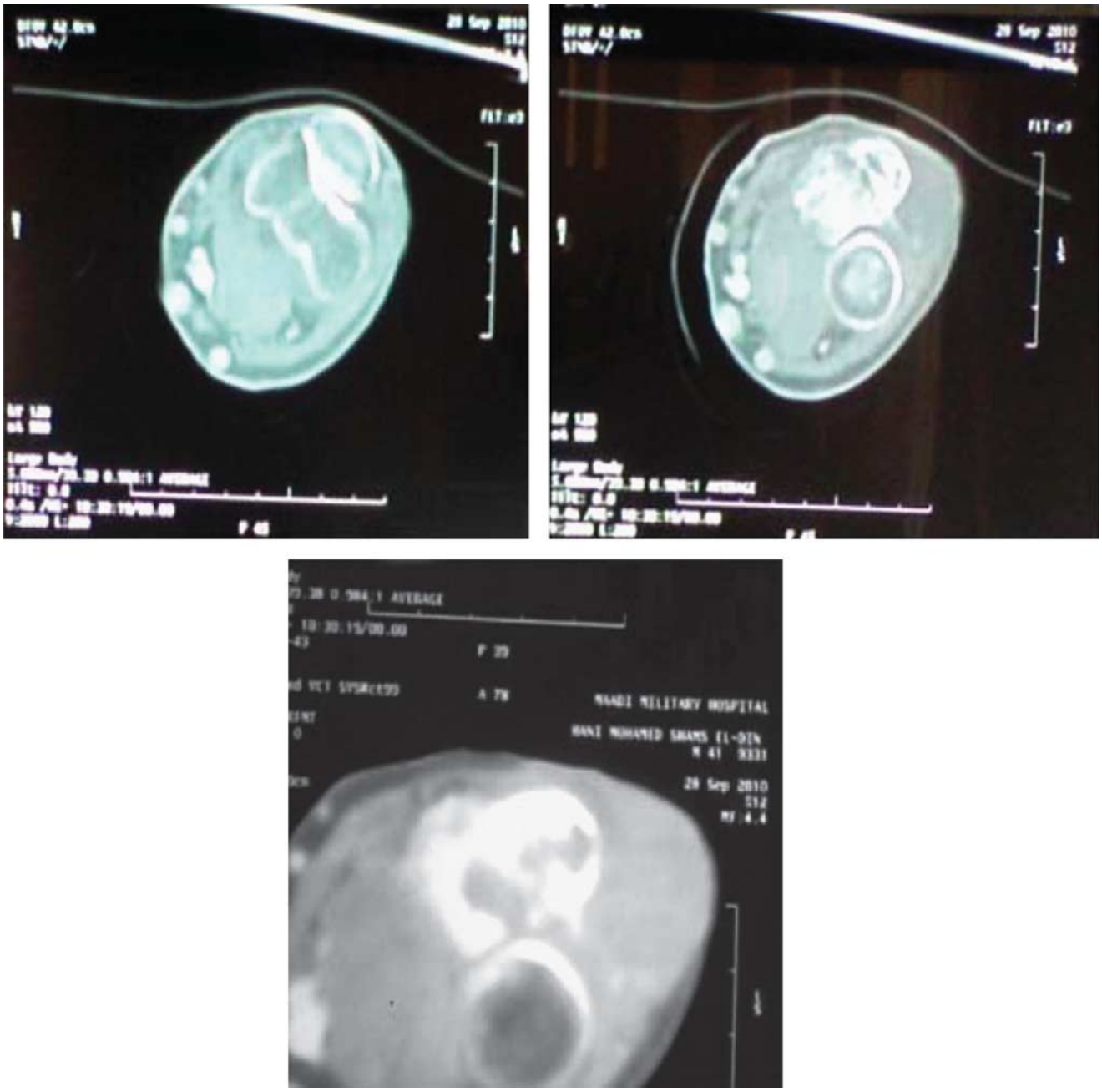
Figure 2

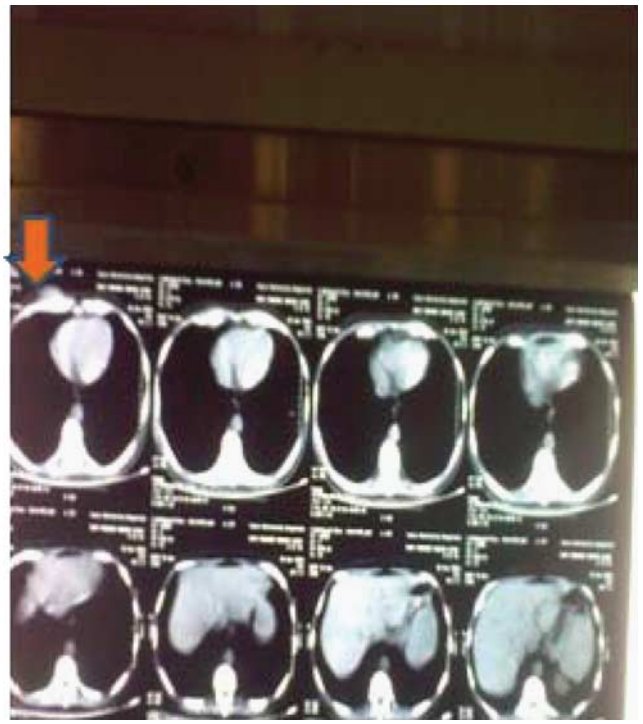


Large soft tissue mass destroying distal two-third of the radius and upper one-third of the ulna.

including exophthalmos, xanthelasma, interstitial lung disease, retroperitoneal fibrosis, pituitary, hypothalamic infiltration, and central nervous system and cardiovascular involvement [1].

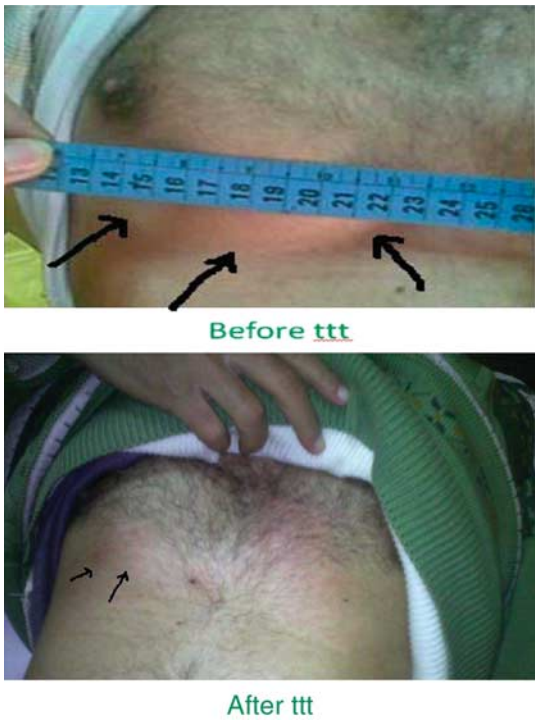
Histologically, ECD is characterized by the presence of 'foamy' histiocytes, which stain positive for CD68 but negative for CD1a and S100; on ultrastructural examination, these cells do not show Birbeck granules [5]. In addition, there is a chronic inflammatory infiltrate composed of plasma cells, lymphocytes, Touton giant cells, and multinucleated giant cells that are produced by aggregation of macrophages [3]. There is no standard treatment for ECD owing to its rarity, whereas several options including steroids, various cytotoxic agents, and hematopoietic stem cell transplantation have been reported, with variable effects [6]. Bisceglia *et al.* [7] reported that corticosteroids are the traditional first-line treatment and are used to control symptoms, but generally they are either ineffective or only transiently effective. In another study by Jendro *et al.* [8], two patients with ECD presented initially with different clinical symptoms. The first patient had bony pains, predominantly in the legs, whereas in the other patient the symptoms were related to obstruction of both ureters, as in idiopathic retroperitoneal fibrosis. Sequential

Figure 3



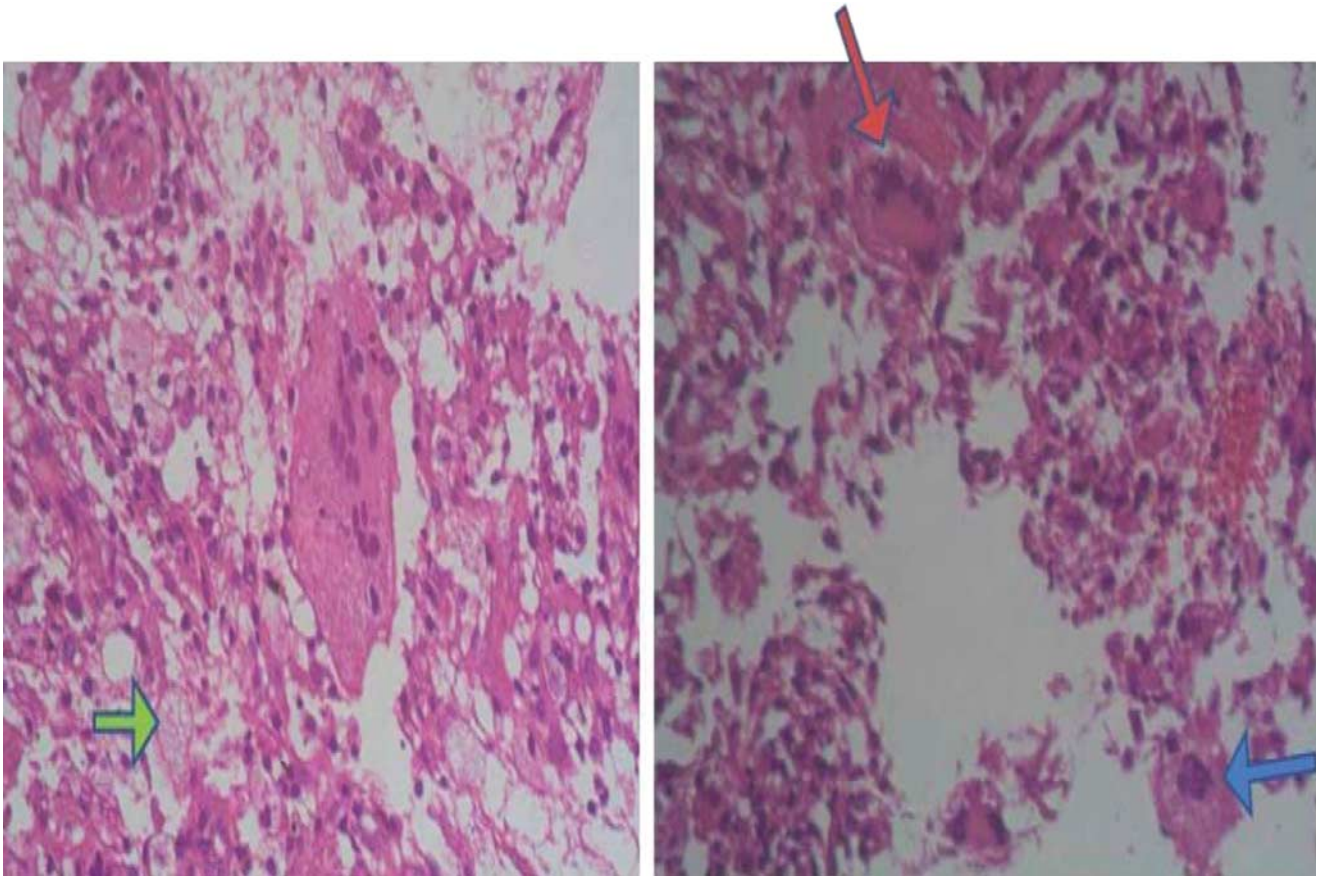
Chest wall swelling (arrow).

Figure 5



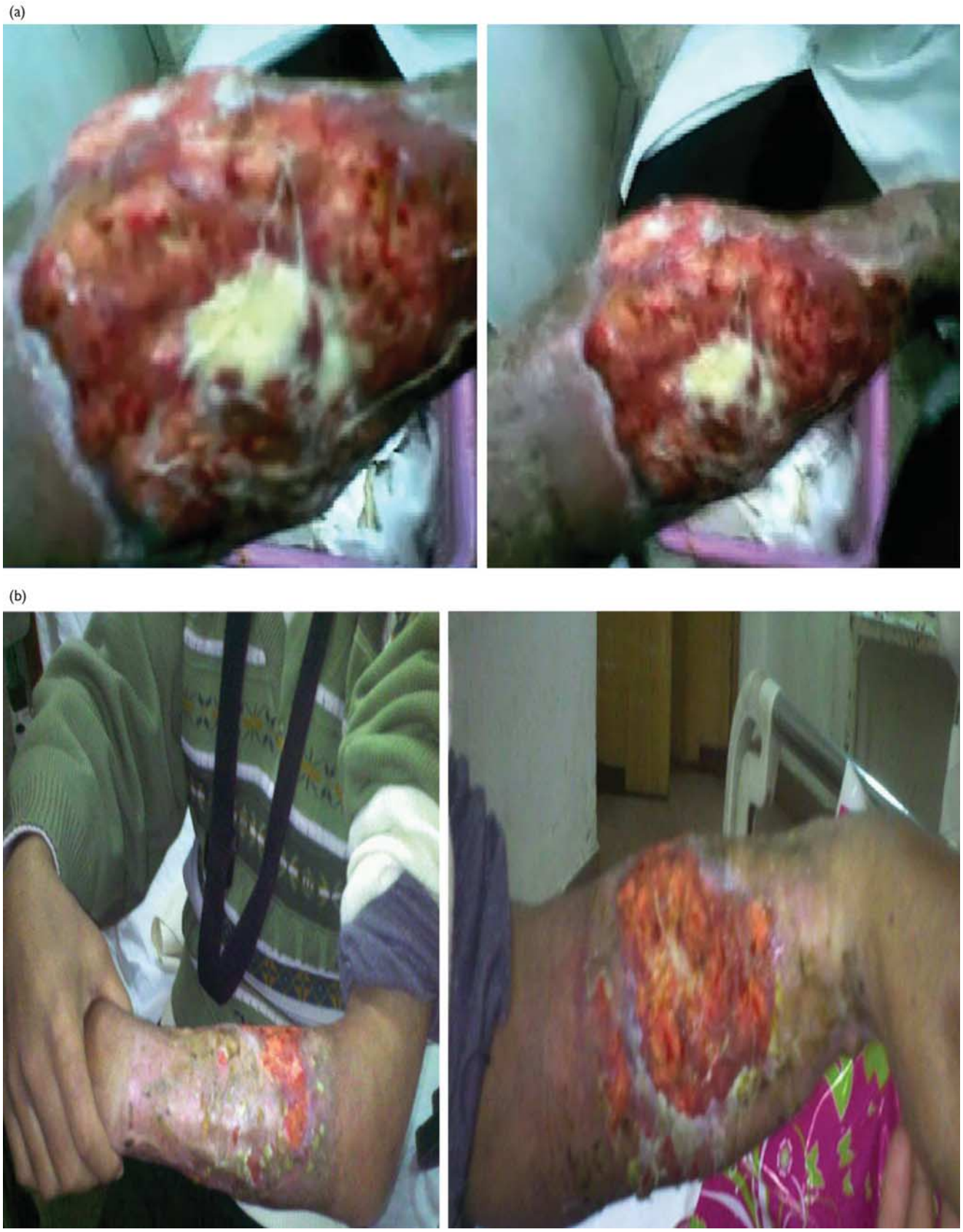
Chest wall swelling before (a) and after (b) treatment.

Figure 4



The histological picture of Erdheim–Chester disease with foam cells (green arrow), Touton giant cells (blue arrow), and multinucleated giant cells (red arrow).

Figure 6



The patient's forearm before (a) and after (b) treatment. (a) The forearm fungating mass before treatment, (b) after 2 months of treatment.

treatment with vinblastine and mycophenolate mofetil, together with prednisolone, was started and a beneficial effect was noted in both patients at follow-up intervals of 15 and 16 months, respectively [8]. Other cytotoxic drugs such as vincristine, adriamycin, and etoposide have been used in different combinations, but often with poor results, and it is reported that a number of deaths in ECD patients treated with such approaches were probably treatment related [9].

According to Mossetti *et al.* [10], bisphosphonates are efficient for the treatment of osteolytic lesions in Langerhans-cell histiocytosis, but have only partial or temporary success in the management of bone involvement in ECD. Cladribine has been used successfully in adult Langerhans histiocytosis, but its application in ECD is limited to two patients, one of whom responded [11]. Braiteh *et al.* [12] described the successful treatment of three patients with ECD with IFN-α and reported that the mechanisms underlying its salutary effects are unclear but could be because of maturation and activation of dendritic cells, immune-mediated (e.g. through natural killer cells) destruction of histiocytes, or direct antiproliferative effects. Radiotherapy had been attempted by Matsui *et al.* [13], who reported a case of a 42-year-old woman who had ECD that showed a gradual response after treatment with radiation therapy. Biological therapy was used by Aouba *et al.* [14], who treated two patients with ECD with poor tolerance or contraindication to IFN-α with anakinra and observed a good response. Sirolimus is an effective drug in oncologic and transplant fields and owing to its immunesuppressive and antiproliferative properties, it was used successfully in autoimmune diseases such as systemic lupus erythematosus, particularly for patients refractory to conventional therapies. Vaglio *et al.* [15] reported a case of an ECD patient who was refractory to different combination therapies (steroids plus tamoxifen, steroids plus cyclophosphamide) and responded well to the association of steroids and sirolimus. Everolimus is a 40-*O*-(2-hydroxyethyl) derivative of rapamycin with immunosuppressant and antiangiogenic properties. In cells, everolimus binds to the immunophilin FK-binding protein-12 to generate an immunosuppressive complex that binds to and inhibits the activation of mTOR. Inhibition of mTOR activation results in the inhibition of T lymphocyte activation and proliferation associated with antigen and cytokine (IL-2, IL-4, and IL-15) stimulation and the inhibition of antibody production [16].

On the basis of the previously reported success of its immunosuppressant and antiangiogenic properties, we used this drug in the treatment of this case after receiving the approval of the medical ethics committee of Internal Medicine Hospital, Cairo University.

We started the treatment on August 2010 with 2.5 mg/day, which was increased to 5 mg/day after 1 week, with good tolerability, but when the dose was increased to 10 mg/day, the patient started to develop nausea and a slight increase in liver transaminases; thus, the patient was maintained on 5 mg/day for 2 months, with marked improvement in the bony pains, complete disappearance of chest wall swellings, and an obvious decrease in the diameter of the fungating mass in the forearm, along with initial healing of the ulcers in the overlying skin, but unfortunately, we could not continue the treatment because of financial constraints (Figs 5 and 6).

Conclusion

ECD is a rare disease with mainly skeletal and sometimes extraskeletal manifestations, but no standard treatment was available until now owing to its rarity. However, the use of everolimus with its immunosuppressant and antiangiogenic properties may make it, besides other medications, namely, low-dose steroids, antiresorptive therapy, and symptomatic analgesia, a useful tool in the management of this rare disease.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Dagna L, Girlanda S, Langheim S, Rizzo N, Bozzolo EP, Sabbadini MG, Ferrarini M. Erdheim–Chester disease: report on a case and new insights on its immunopathogenesis. Rheumatology (Oxford) 2010; 49:1203–1206.

2 Veyssier-Belot C, Cacoub P, Caparros-Lefebvre D, Wechsler J, Brun B, Remy M, *et al.* Erdheim–Chester disease: clinical and radiologic characteristics of 59 cases. Medicine (Baltimore) 1996; 75:157–169.

3 Serratrice J, Granel B, De Roux C, Pellissier JF, Swiader L, Bartoli JM, *et al.* 'Coated aorta': a new sign of Erdheim–Chester disease. J Rheumatol 2000; 27:1550–1553.

4 Pertuiset E, Laredo JD, Lioté F, Wassef M, Jagueux M, Kuntz D, *et al.* Erdheim–Chester disease: report of a case, review of the literature and discussion of the relation to Langerhans-cell histiocytosis. Rev Rhum Ed Fr 1993; 60:601–609.

5 Cline MJ. Histiocytes and histiocytoses. Blood 1994; 84:2840–2853.

6 Gaspar N, Boudou P, Haroche J, Wechsler B, Van Den Neste E, Hoang-Xuan K, *et al.* High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for adult histiocytic disorders with central nervous system involvement. Haematologica 2006; 91:1121–1125.

7 Bisceglia M, Cammisa M, Suster S, Colby TV. Erdheim–Chester disease: clinical and pathologic spectrum of four cases from the Arkadi M. Rywlin slide seminars. Adv Anat Pathol 2003; 10:160–171.

8 Jendro MC, Zeidler H, Rosenthal H, Haller H, Schwarz A. Improvement of Erdheim–Chester disease in two patients by sequential treatment with vinblastine and mycophenolate mofetil. Clin Rheumatol 2004; 23:52–56.

9 Egan AJ, Boardman LA, Tazelaar HD, Swensen SJ, Jett JR, Yousem SA, Myers JL. ECD: clinical, radiological and histopathologic findings in 5 patients with ILD. Am J Surg Pathol 1999; 23:17–26.

10 Mossetti G, Rendina D, Numis FG, Somma P, Postiglione L, Nunziata V. Biochemical markers of bone turnover, serum levels of IL6/IL6 soluble receptor and bisphosphonate treatment in ECD. Clin Exp Rheumatol 2003; 21:232–236.

11 Myra C, Sloper L, Tighe PJ, McIntosh RS, Stevens SE, Gregson RHS, *et al.* Treatment of Erdheim–Chester disease with cladribine: a rational approach. Br J Ophthalmol 2004; 88:844–847.

12 Braiteh F, Boxrud C, Esmaeli B, Kurzrock R. Successful treatment of Erdheim–Chester disease, a non-Langerhans-cell histiocytosis, with interferon. Blood 2005; 106:2992–2994.

13 Matsui K, Nagata Y, Hiraoka M. Radiotherapy for Erdheim–Chester disease. Int J Clin Oncol 2007; 12:238–241.

14 Aouba A, Georgin-Lavialle S, Pagnoux C, Silva NM, Renand A, Galateau-Salle F, *et al.* Rationale and efficacy of interleukin-1 targeting in Erdheim–Chester disease. Blood 2010; 116:4070–4076.

15 Vaglio A. A pilot study in the treatment of ECD. ERA-EDTA 2004;75–76.

16 Goudar R, Shi Q, Hjelmeland M, Keir ST, McLendon RE, Wikstrand CJ, *et al.* Combination therapy of inhibitors of epidermal growth factor receptor/vascular endothelial growth factor receptor 2 (AEE788) and the mammalian target of rapamycin (RAD001) offers improved glioblastoma tumor growth inhibition. Mol Cancer Ther 2005; 4:101–112.