Annals of Hematology (2019) 98:227–230
https://doi.org/10.1007/s00277-018-3421-7

LETTER TO THE EDITOR

Long-term remission of refractory Rosai-Dorfman disease after salvage therapy with clofarabine in an adult patient

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Received: 23 May 2018 / Accepted: 27 June 2018 / Published online: 6 July 2018

Dear Editor,

Rosai-Dorfman disease (RDD, sinus histiocytosis with massive lymphadenopathy) is a rare idiopathic nonmalignant histiocytic disorder. RDD occurs typically in children, adolescents, or young adults presenting with massive cervical lymphadenopathy, fever, and laboratory abnormalities including leukocytosis, polyclonal hypergammaglobulinemia, anemia, and elevated acute phase parameters [1, 2]. While pathogenesis of RDD remains largely unknown, a growing body of evidence proposes a disturbance of microenvironmental homeostasis combined with inherited genetic alterations in the Ras-Raf-MEK-ERK signal transduction pathway as an important etiological factor [3, 4]. In patients with severe symptoms or systemic involvement, corticosteroids have frequently been used as first-line therapy [5–7]. In steroid-refractory RDD, a variety of immunomodulatory and chemotherapeutic agents including rituximab, interferon, imatinib, or alkylating agents have been used with disappointing results [8–11]. Here, we present the first case of a refractory RDD with a long-term remission after a salvage therapy with clofarabine.

A 25-year-old male was admitted to our hematology department with recurrent episodes of fever, arthralgias, cutaneous nodules, and massive enlargement of cervical lymph nodes (Fig. 1a–c). Laboratory tests revealed a leukocytosis of 12,030/μL as well as elevated C-reactive protein plasma levels (14–16 mg/dL). Evaluation for rheumatoid and antinuclear factors and laboratory testing for standard tumor markers as well as HIV, HHV-6, EBV, or CMV remained negative. Upon detection of S-100-, CD68-, and CD163-positive histiocytes exhibiting emperipolesis in a biopsy of enlarged adenoid tissue from the nasal cavity, the diagnosis of RDD with cervical lymphadenopathy and extranodal involvement was established (Fig. 1). A BRAF V600E mutation, which can be frequently observed in LCH and Erdheim-Chester disease (ECH), could not be detected [12, 13].

A first-line therapy with corticosteroids (dexamethasone 40 mg qd) resulted in a minor regression of the cervical lymphadenopathy with an early relapse accompanied by fever and massive weight loss of 15 kg within 9 weeks. Disease progression was confirmed by FDG-PET-CT scan showing multiple bone lesions and progressive cervical, axillary, and mediastinal lymphadenopathy (Fig. 2). A salvage therapy with four doses of rituximab (375 mg/m^2 q3w) as well as a treatment with imatinib (400 mg qd) was unfortunately ineffective. Since in our patient with an extended disease stage no BRAF V600E mutation could be detected, a targeted therapy with a BRAF/mitogen-activated protein kinase pathway inhibitor was not initiated.

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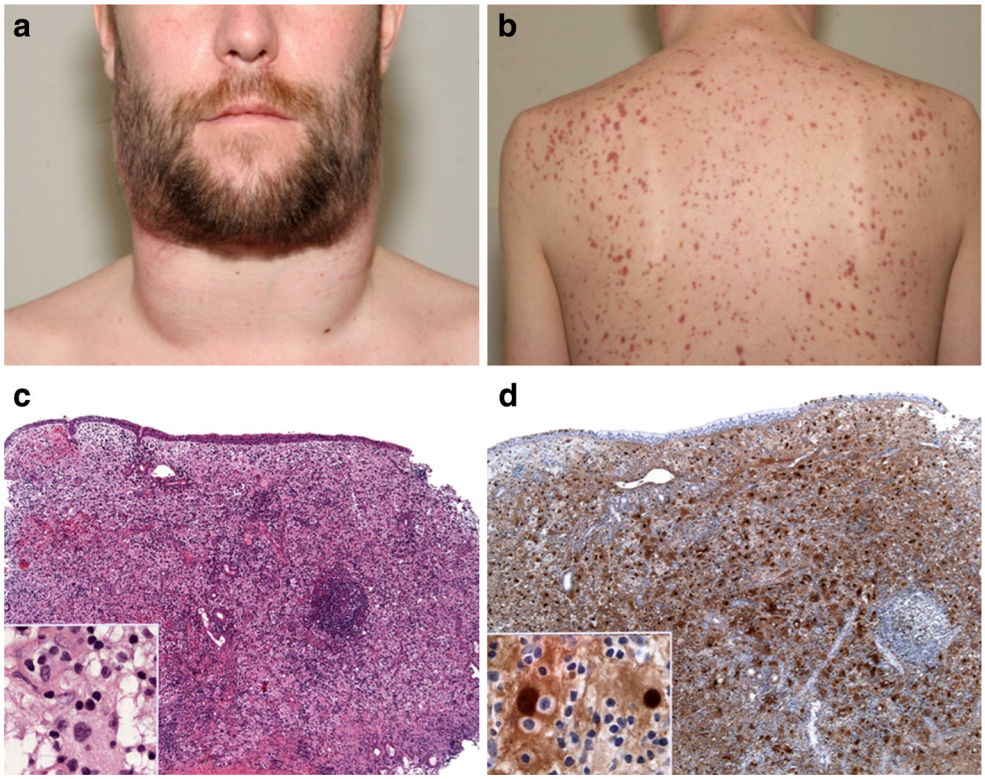

Fig. 1 Clinical and histopathological presentation of RDD in a 25-year-old patient. **a** Clinical presentation of RDD with massive indolent cervical lymph node enlargement. **b** Cutaneous manifestations of RDD (papules and multiple nodules). **c** Paranasal sinus biopsy covered by respiratory cylindrical epithelium. Underneath the epithelium, numerous histiocytes with abundant slightly eosinophilic cytoplasm admixed with lymphocytes and plasma cells can be seen (H&E, × 50). The histiocytes show numerous intact lymphocytes within their cytoplasm (emperipolesis or lymphocytophago-cytosis) (inset, H&E, × 400). **d** S-100 stain demonstrates that the histiocytes are strongly and homogeneously positive (immunoperoxidase, × 50). High-power view shows the strong immunoreactivity of the histiocytes for S-100 protein characteristic of Rosai-Dorfman disease (inset, immunoperoxidase, × 400)

Finally, the patient presented with rapid clinical deterioration accompanied by significant progression of lymphadenopathy, newly diagnosed kidney involvement, and an additional bone marrow infiltration. Ultimately, a salvage therapy with clofarabine (25 mg/m^2/day × 5 days/cycle q28d) was initiated. Remarkably, after only two courses of clofarabine a substantial regression of cervical lymphadenopathy could be observed. This was accompanied by the disappearance of the B symptoms and a significant improvement of overall condition. A PET/CT scan showed a massive regression of all extranodal manifestations and a nearly complete regression of all nodal involvements with minimal remaining activity. Clofarabine was well tolerated, but resulted in temporary pancytopenia with repeated need for transfusions and G-CSF support. After six courses, the patient shows an excellent physical condition and a complete remission of nodal and extranodal manifestations with entirely normalized hematological parameters 45 months after the completion of clofarabine treatment.

Here, we present the first case of a long-term remission after a clofarabine salvage therapy in an adult with multilocular refractory RDD. With neutropenia and thrombocytopenia requiring frequent transfusions, the toxicity profile of clofarabine occurred as previously observed [14]. Two case series including children and young adolescents with recurrent or refractory histiocytosis (of which four patients suffered from refractory RDD) receiving a clofarabine salvage therapy have been reported so far [14, 15]. Although the ORR was 85%, only two out of four children with RDD showed a complete resolution of their disease symptoms after six cycles of clofarabine.

In conclusion, this case demonstrates that clofarabine is a highly effective salvage therapy for multilocular refractory RDD in adults. Nevertheless, further prospective clinical trials are needed to accurately determine the efficacy,

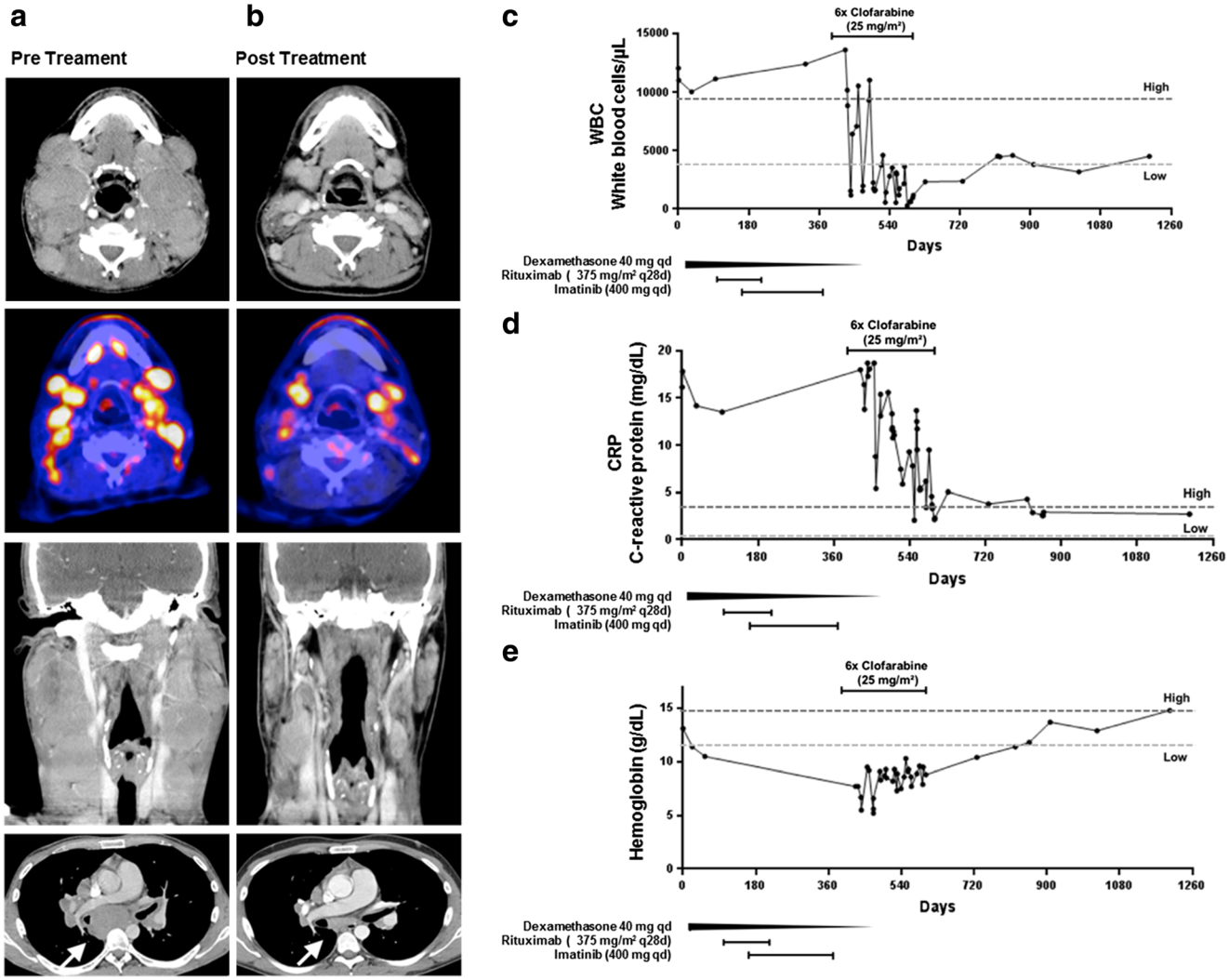

Fig. 2 CT and 18F-FDG-PET/CT scan before and after salvage treatment with clofarabine. **a** CECT (upper row) and 18F-FDG-PET/CT (lower row) of the neck shows massively enlarged cervical nodes with initially strong FDG uptake involving all nodal levels (left). **b** After six cycles clofarabine, there are only residual nodes left and FDG uptake showed markedly declined. **c**–**e** CRP, WBC, and hemoglobin levels during the entire treatment

optimal dosing, and long-term toxicity of clofarabine in refractory RDD.

Contributions MM and CRG prepared the manuscript assisted by CH. HGK, MH, LQMF, MH, and SW made clinical data available. CH, MS, KM, KPK, and JH extracted the medical records. CH, MS, and DD prepared the first draft of the manuscript. LK gave important advice during the treatment of the patient and the preparation of the manuscript. All authors had access to the data and a role in writing this manuscript.

Compliance with ethical standards

After obtaining written informed consent from the patient, this case study was performed in accordance with the Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

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