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CASE BASED REVIEW

Clinical presentation, imaging and response to interferon-alpha therapy in Erdheim–Chester disease: case-based review

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Abstract

Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis associated with BRAFV600E mutations in more than 50% of cases and presenting with 95% with skeletal lesions. However, cutaneous, pulmonary, large vessels and central nervous system involvement can also occur. We report a case of a 25-year-old woman who was admitted in 2018 for exploration of diffuse bone pain and rashes on the face. Her current symptoms had started 14 months earlier and consisted of bone pain, affecting the legs. She had periodic low-grade fever, asthenia and xanthelasma-like papules appeared on face. At admission, physical examination showed bilateral and symmetrical long bone pain, especially in the knees and multiple xanthelasma-like papules around the eyelids, cheeks and chin. Laboratory tests revealed elevated erythrocyte sedimentation rate and C-reactive protein. Magnetic resonance (MR) imaging showed multiple mixed bone lesions with a hyperintensive MR signal on PD FS and hypointense signal on T1of the femur and tibia. Bone scintigraphy indicated bilateral and symmetrical metaphyseal and diaphyseal increased uptake. Abdominal computed tomography (CT) scan showed infiltration of the perirenal fat. Biopsy of the skin revealed histiocytic infiltration, which was CD68-positive and CD100-positive, confirming the diagnosis of ECD. Patient was treated with interferon-α (IFN-α) plus methylprednisolone. After 6 months of treatment her clinical condition partly improved: a reduction of pain on visual analogue scale (VAS) scale, significant decrease of methylprednisolone dose and specific dynamics according to bone MR imaging data, however, no change in symptoms attributed to skin rash was noted. We also provide the literature review results of IFN-α treatment efficacy in Erdheim–Chester disease involving the skin and musculoskeletal system with MR imaging changes.

Keywords Erdheim–chester disease · Bone lesions · Xanthelasma-like eruption · Magnetic resonance imaging · Interferon-α

Introduction

ECD is a rare clonal disorder of unknown etiology, characterized by chronic uncontrolled inflammation and organ infiltration by CD68+, CD1a−non-Langerhans foamy histiocytes surrounded by fibrosis [1–3]. The disease typically presents with bone involvement, but every organ and tissue can be affected including multisystemic, life-threatening forms [4]. ECD is observed more frequently in males between the age of 40 and 70 years [5].

The main radiographic findings of disease include bilateral, symmetric diametaphyseal sclerosis of the long bones, which on MR manifest as extensive replacement of the fatty marrow by low signal on T1WI, heterogeneous signal on T2WI/STIR and enhancement after gadolinium injection [1, 6, 7]. In addition to osteosclerosis a mixed pattern with lytic and sclerotic lesions are the rarely skeletal manifestations

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of ECD [1, 8]. The place of MR imaging in the diagnosis, response to treatment or prognosis assessment is still discussed [9–11].

Currently, the first-line therapy with the largest amount of supporting evidence in ECD is IFN-α and pegylated IFN-α (PEG-IFN-α) (Grade C2) [2]. In the largest single series, a prospective, nonrandomized, observational cohort study of 53 ECD patients, 46 patients treated with IFN-α or PEG- IFN-α significantly improved overall survival compared with other therapies and was an independent predictor of improved survival in multivariate analysis [5]. The efficacy of IFN-α was dependent on the organ involved and the dose regimen [12]. Various second line treatments such as kinase inhibitors (vemurafenib, cobimetinib) [13–16], biologics (anakinra, infliximab, tocilizumab) [17–20] and others (cladribine) [21] are suitable for treatment ECD after IFN-α failure or intolerance, or in case of life-threatening manifestations.

Here, we report a clinical case of ECD with positive clinical dynamics of pain syndrome, description of MRI changes in bone tissue without improving of skin lesions on IFN-α treatment and perform a review on the published cases for response to IFN-α treatment of ECD.

Case report

A 25-year-old woman came to our hospital with complains of pain and swelling of the both knees, right elbow and right ankle joints accompanied by an increase in skin temperature, diffuse bone pain in the bones of the upper and lower extremities, low-grade fever, a rash around the eyes and the general weakness. On presentation (14 month ago), she had only pain and limitation of movement in the knee joint after undergoing rotavirus infection, but no other discomforts. One month later, fatigue and leg pain slowly developed accompanied by episodes of fever and yellowish peri-orbital xanthelasma-like lesions were apparent. Initially the pain appeared after exercises with the normalization after rest. It had escalated over several months and progressed to constant bone pain. She was prescribed ibuprofen without effect. Laboratory analysis (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), rheumatoid factor (RF), uric acid level and an antistreptolysin O were normal. Abdominal CT revealed an infiltration of the perirenal fat. There were no changes on the chest CT. MRI of left knee showed multiple focal bone marrow lesions which hyperintensive on PD FS (Fig. 1a) hypointensive on T1WI of the femora and tibiae (Fig. 1b).

2 months late forearm pain developed, first in the left and then in both. 6 weeks after that laboratory findings disclosed the following: ESR—32 mm/h (normal 0–20 mm/h); CRP—18.36 mg/L (normal $\leq$6 mg/L), total serum protein—55.7 g/L, albumin 31.0 g/L. Other routine biochemical tests, including liver and renal function tests, were normal. Total calcium—2.03, serum 25-hydroxyvitamin D—36.79, parathormone—22.3, Ca ionized—1.2, phosphorus—1.2. The autoantibody screen was negative (rheumatoid factor, and antinuclear, anti-dsDNA, anti-Sm, anti-SSA(Ro), anti-SSB(La), anti-RNP, anti-topoisomerase I (Scl-70), anti-Jo1, anti-Mi2, anti-Ku, anti-PM-Scl, anti-PL-7, anti-PL-12, anti-Ro-52 and anti-neutrophil cytoplasmic antibodies).

There were no changes on electromyography and radiography of the skull. Technetium-99 m bone scintigraphy showed symmetric and abnormally increased metaphysodiaphyseal labeling of the long bones, predominantly in the lower limbs (Fig. 2).

She was treated with methylprednisolone 8 mg per os daily during 4 weeks without improvement of clinical symptoms.

The patient was referred for consultation to a rheumatologist in our clinic. The patient's temperature was 37.4 °C, there was a diffuse pain in the upper and lower extremities, yellowish xanthelasma-like lesions on the face and fatigue. Physical examination revealed a tenderness and limitation of movement in the knee and elbow joints, tenderness to percussion of adjacent bones and multiple small yellow-orange papules on the both temples, both lower and upper eyelids, both cheeks and chin (Fig. 3a, b).

Due to the presence of bone pain in combination with xanthelasmas on the face, changes in MR imaging and Technetium-99m bone scintigraphy a diagnosis of histiocytosis was suspected and biopsy of the skin lesion on the face was performed. Histological analysis revealed chronic inflammatory infiltrates, primarily lymphocytes, lymphohistiocytic infiltrates around the vessels with granuloma formation. Histiocytes were positive for CD68 immunostains (Fig. 4a), positive for S-100 (Fig. 4b) and completely negative for CD1a.

The biopsy findings and imaging features were considered diagnostic of ECD. The patient was treated with IFN-α (9 mIU/week) and daily oral methylprednisolone at a dose of 8 mg daily for 3 months, the dose was tapered to 4 mg for 2 months and to 2 mg daily. After 6 months of treatment, the patient pain VAS decreased from 98 to 5 mm, inflammatory markers were normal, but skin lesion remained unchanged. Follow-up MR images were obtained 1 month and 6 months after the treatment beginning. The cortical bone thickness of the distal femur and bone marrow infarcts in the epiphysis of the tibia and femur appeared on the follow-up MR images. After 6 months of treatment T1-weighted images of the knee showed decreased lesion intensity in the metadiaphyses of the tibia and femur (Fig. 1c–f). Because there was no skin improvement, the BRAF V600 mutation analysis was performed

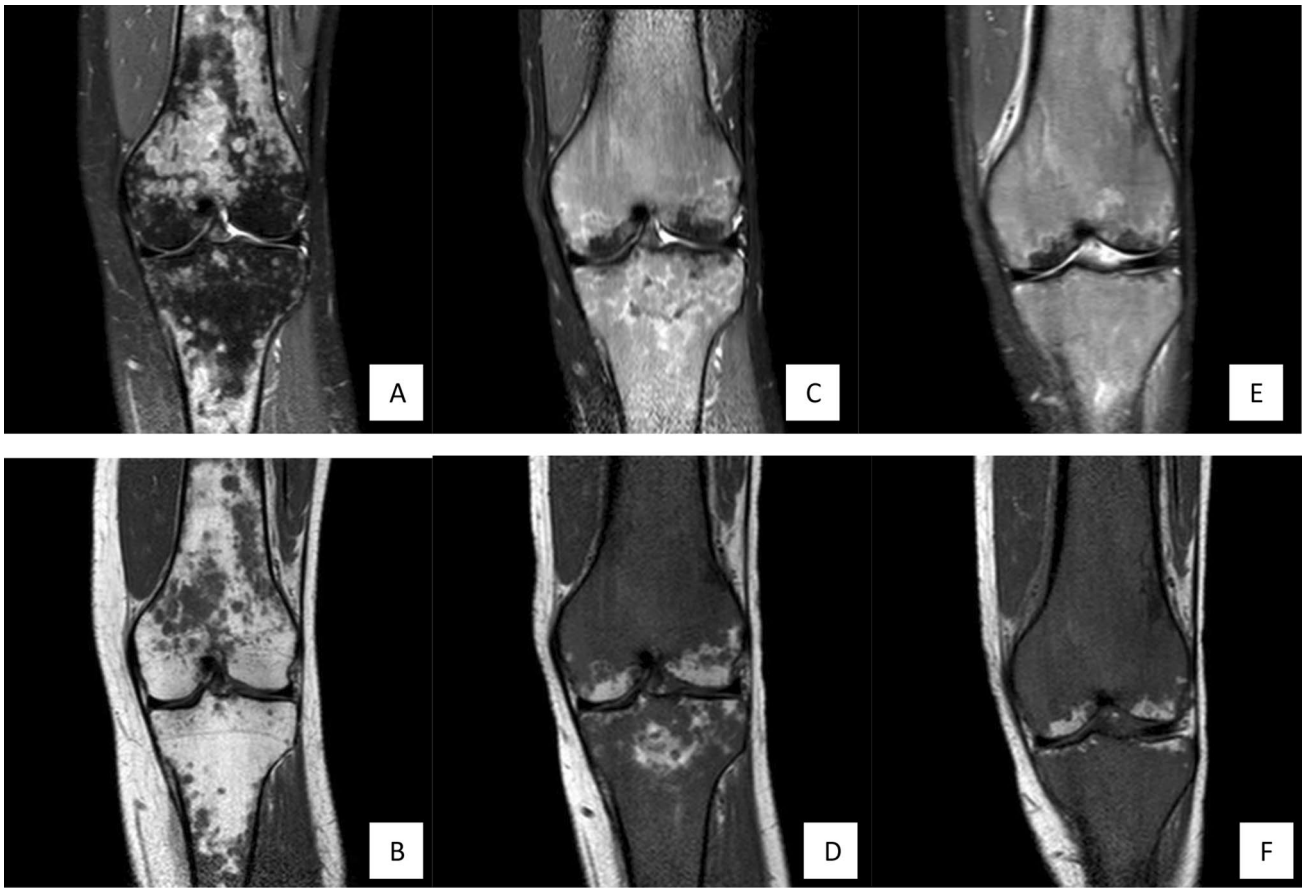

Fig. 1 MRI of the left knee showing multiple focal bone marrow lesions which hyperintensive on PD FS (**a**) hypointensive on T1WI (**b**) and no bones cortical thickness before treatment (**a**, **b**); diffuse bone marrow lesions, femur cortical thickness and osteonecrosis areas (**c**, **d**) 1 month after the treatment with IFN-α beginning; diffuse bone marrow lesions become less intensive, femur cortical thickness and osteonecrosis areas (**e**, **f**) 6 months after the treatment with IFN-α

for evaluation the possibility of vemurafenib treatment. The result was negative, that's why the question of further therapy remained open.

Timeline of clinical features and interventions are summarized in Fig. 5.

Search strategy

Data sources and searches

We searched PubMed, Web of Science and Scopus for cases of IFN-α treatment of Erdheim–Chester disease involving the skin and musculoskeletal system with MR imaging changes published in English up to August 1st, 2019. The search terms were interferon-α, Erdheim–Chester disease, musculoskeletal system, skin and MR imaging. We reviewed the abstracts of relevant studies and retrieved appropriate articles.

Study selection

We scanned the titles and abstracts for the following inclusion criteria: case reports and observational cohort study of Erdheim–Chester disease treated with IFN-α, published in English language, and published in a peer-reviewed journal. Reviews and other study types lacking clinical data from individual patients were excluded.

Data extraction and study quality assessment

We extracted the following data using a form: author, publication year, numbers of patients, clinical history, histopathologic features (BRAF V600 mutation), treatment, and outcomes [22].

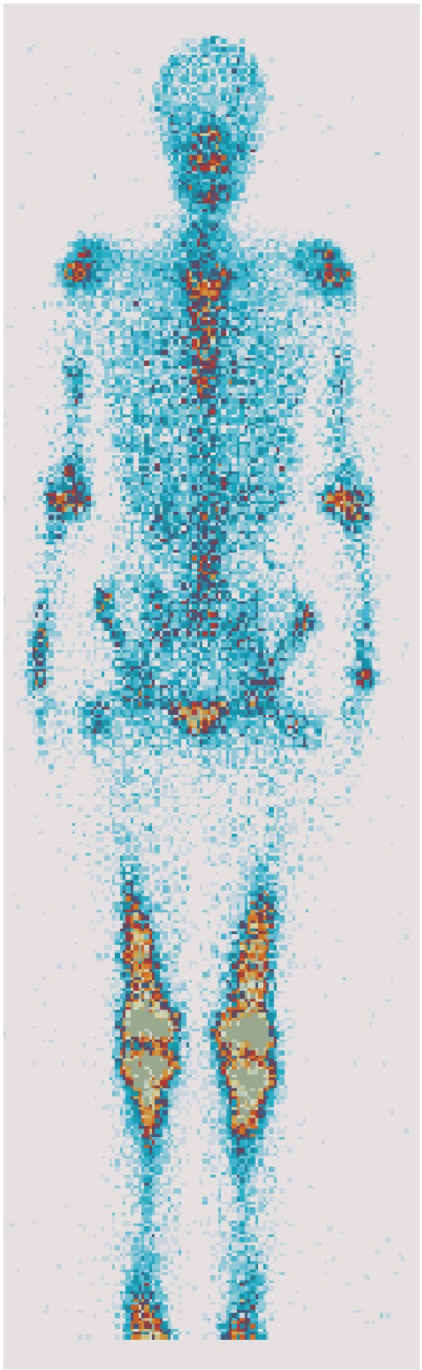

Fig. 2 Bone scan showed multiple increased uptakes in both maxillae, mandible, both humerus, both radii, both ulnae, both distal femurs, both proximal and distal tibiae

Results

We have found 57 articles about Erdheim–Chester disease treated with IFN-α, published in English language. In addition to our case, 6 articles about outcome of skin involvement in ECD treating with IFN-α were identified by the literature review (Table 1). In general, five case reports and one observational cohort study were included into the analysis. The total number of patients was 17. Among case reports only in one patient was noted worsening of skin lesions during treatment with IFN-α in combinations with cyclosporine and high-dose corticosteroids. Observational cohort study by Hervier et al., showed 71% response of skin manifestation to high-dose IFN-α, in 1 patient—worsening, and in 1 patient—without dynamics.

The two clinical cases of pediatric ECD patients with follow-up MR imaging of the skeleton during treatment were described in the literature. Joo and Go [10] performed a follow-up MR examination of the knee to observe the marrow changes after 8 and 15 months. They have demonstrated with sequential MR imaging restoration of normal marrow signal in a pediatric patient diagnosed with ECD treated with glucocorticoids. White and Silvester [9] report a case of ECD in a 15-year-old boy with central nervous system involvement and skeletal findings. MR imaging demonstrates decreased lesion enhancement after 3 months of treatment with interleukin-1 receptor antagonist (anakinra) and vinblastine. There are no data about follow-up skeleton MR imaging in adult ECD patients treated with IFN-α.

Discussion

ECD is rare non-Langerhans histiocytosis disorder with foamy lipid-laden histiocytes ranging from asymptomatic osteosclerosis to multisystemic manifestations with involvement of central nervous, cardiovascular, renal, retro-orbital, integumentary, endocrine, and respiratory systems [2]. The skeleton changes occur in up to 96% of ECD patients, however, only half of the patients report bone pain, usually around the knees and ankles [23, 24]. The most common skin manifestation of ECD is xanthelasmas, which occurs in 33% of patients.[2, 25, 26]. Atypical skin lesions included red-brown pinpoint papules on the face or brown–red slightly pruritic papules on the trunk [27, 28].

Our patient has a typical clinical manifestation of ECD: bone pain around the knees with future involvement of ankles, elbows and peri-orbital xanthelasma-like skin lesions. However, she is younger than the average ECD patient, and she presented with mixed osteosclerosis and osteolytic lesions due to MR imaging data instead of the classical bilaterally and symmetrically osteosclerosis in the diametaphyseal regions of the long bones. The lytic lesions either on the flat bones, like the ribs and skull, or on the long bones have been previously described by Veyssier-Belot et al. [1]. Typical and atypical EDC lesions may present in atypical foci (axial skeleton and epiphyseal regions) [29, 30, 31].

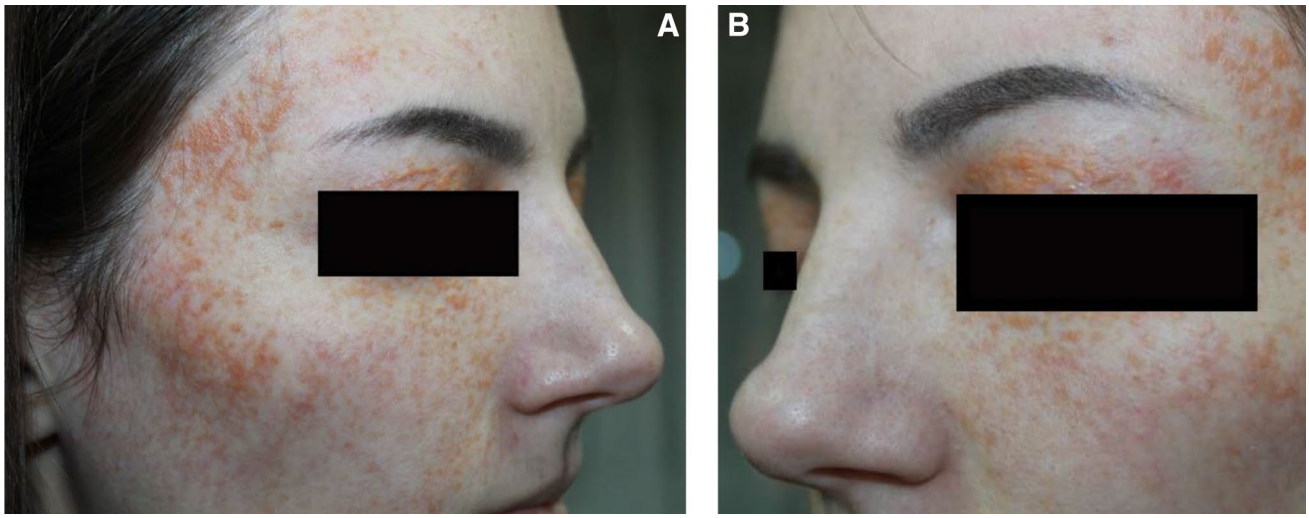

Fig. 3 **a**, **b** Multiple small yellow-orange papules on the both temporal areas, both lower and upper eyelids and around the lips

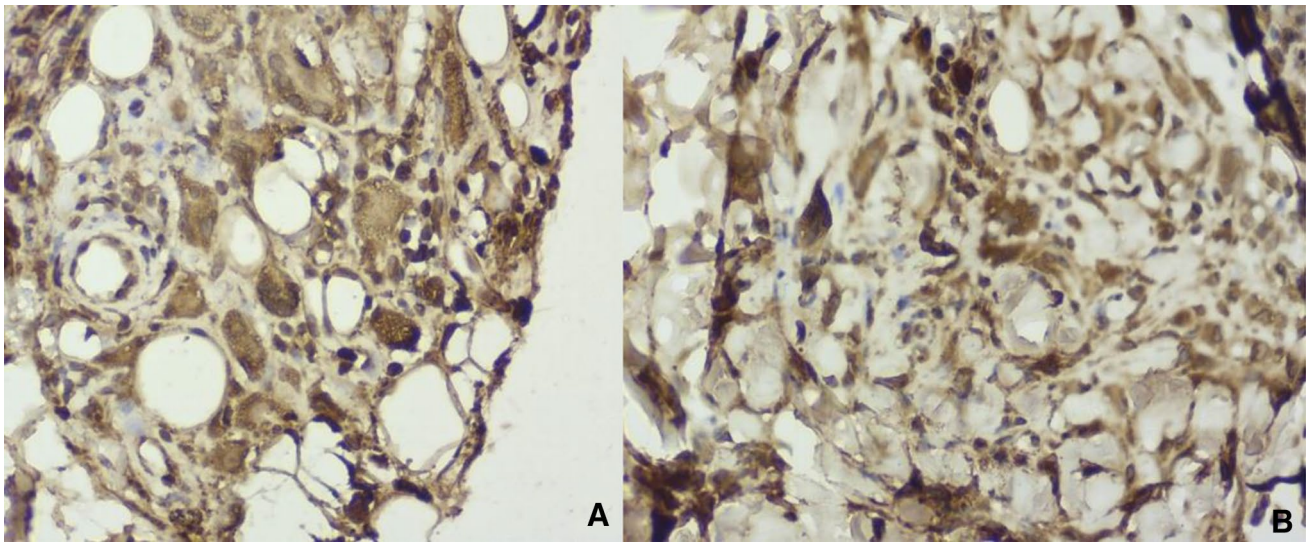

Fig. 4 Histopathological examination of a face skin lesion. **a** CD68 + histiocytes (magnification 40×). **b** S-100–histiocytes (magnification 40s×)

The follow-up MR images of our patient showed cortical bone thickness of the distal femur and bone marrow infarcts in the epiphysis of the tibia and femur. After 6 months of treatment T1-weighted images of the knee showed decreased lesion intensity in the metadiaphysis of the tibia and femur, which correlated with decrease of bone pain.

ECD is difficult to diagnose on imaging due to its variable manifestations, generally nonspecific findings, and its rarity. The optimal use of imaging in the diagnosing, staging, and follow-up of this unusual condition has not yet been determined [32]. The Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan was reported to be a good indicator of disease activity and responses to long-term high-dose IFN-α treatment [33, 34]. The FDG-PET is high cost method. That's why MR imaging could be the alternative method to evaluate the response of treatment in ECD patients with skeletal involvement.

Treatment is suggested for all, but asymptomatic patients without neurologic involvement can undergo expectant observation with medical follow-up every 3–6 months [2]. ECD is a slowly evolving histiocytosis and improvement under treatment usually leads only to partial remission, rather than complete recovery [35–39]. For patients with multisystemic involvement and BRAF-VE600E + mutations, first-line treatment includes usage of INF-α or BRAF inhibitors such as vemurafenib [2]. In our case, the patient was BRAF-VE600E mutations negative and was treated with IFN-α during 6 months with partly improving: a reduction

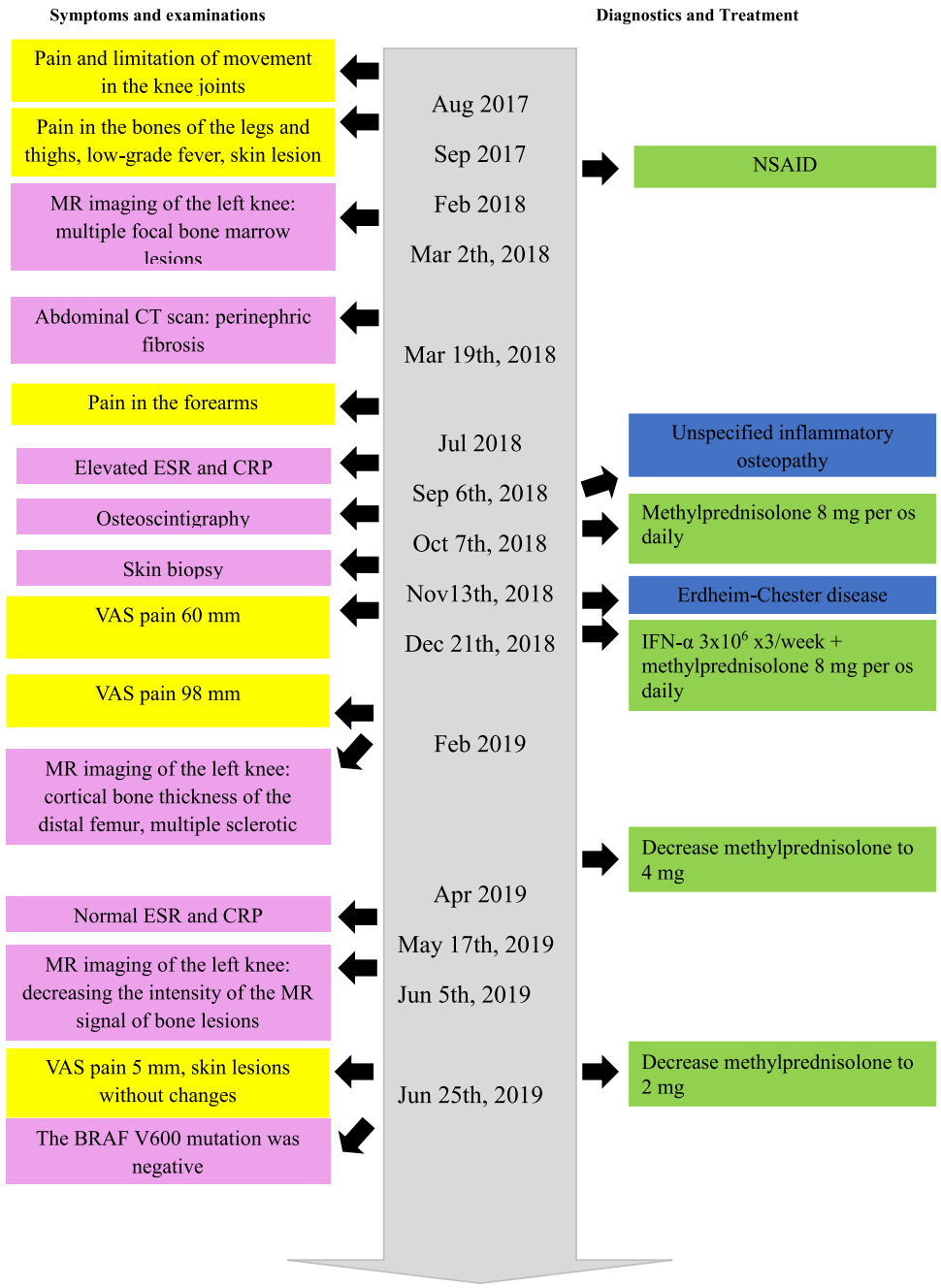

Fig. 5 Timeline of clinical features and interventions

of pain on VAS scale and specific dynamics according to MR imaging data, but no change of skin manifestation. Due to literature date only one patient was noted worsening of skin lesions during treatment with IFN-α in combination with cyclosporine and high-dose corticosteroids [40]. The response to IFN-α treatment was the most prominent in the cutaneous foci of the disease (71%), followed by involvement of the central nervous system, pituitary, lungs and heart, which comprise the foci that are more resistant to treatment [12].

Table 1 The summary of the articles

Authors	Year	Numbers of patients	BRAF V600 mutation	Dose and treatment regimen	Duration of follow-up period (months)	Outcome of skin involvement
Braiteh et al. [36]	2005	1	UN	$6\times10^6\times3$/week 6 months, $3\times10^6\times3$/week 4 months, $1\times10^6\times3$/week	16	Improving, but relapse after treatment discontinuation
Mazor et al. [41]	2014	1	+	$6\times10^6\times3$/week $3\times10^6\times3$/week	6	Improving
Myoung-Shin Kim et al. [42]	2010	5	UN	$6\times10^6\times3$/week	16	Improving
Haroche et al. [37]	2006	2	UN	$9\times10^6\times3$/week $3\times10^6\times3$/week	43	Improving in 6 months, but relapse 25 months after treatment discontinuation
Skinner et al. [40]	2011	1	UN	$3\times10^6\times3$/week + cyclosporine and high-dose corticosteroids	3	Worsening
Hervier et al. [12]	2012	7	UN	PEG-IFN-α or IFN-α 18×10^6/week	36	Improving in 71%, in 1 patient—worsening, and in 1 patient—without dynamics

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Compliance with ethical standards

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

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Authors fulfilled the ICMJE authorship criteria.

Informed consent Written informed consent was obtained from the patient prior to submission of this article for consideration as a case-based review.

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