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Rare diseases of bone: Erdheim-Chester and Rosai-Dorfman non-Langerhans cell histiocytoses

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- Non-Langerhans cell histiocytosis (N-LCH) summarizes a group of rare diseases with different clinical presentations, pathogenesis and morphology. These include primary cutaneous N-LCH, cutaneous N-LCH with systemic involvement, and primary extracutaneous systemic forms with occasional cutaneous involvement.
- The juvenile (JXG) and non-juvenile xanthogranuloma (N-JXG) family of histiocytoses are N-LCH: the JXG family consisting of the JXG (cutaneous), xanthoma disseminatum (cutaneous and systemic) and Erdheim-Chester disease (ECD; systemic); and the N-JXG family consisting of the solitary reticulohistiocytoma (cutaneous), multicentric reticulohistiocytosis (cutaneous and systemic) and Rosai-Dorfman disease (RDD; systemic).
- ECD is a clonal disorder from the JXG family of N-LCH; RDD is a reactive proliferative entity from the non-juvenile xanthogranuloma family of N-LCH.
- ECD and RDD N-LCH are rare disorders, which are difficult to diagnose, with multi-organ involvement including bone and systemic symptoms, and which respond to therapy in an unpredictable way.
- The key to successful therapy is accurate identification at tissue level and appropriate staging. Patients should be observed and monitored in a long-term pattern. Prognosis depends on disease extent and the organs involved; it is generally good for RDD disease and variable for ECD.

Keywords: Erdheim-Chester disease; Rosai-Dorfman disease; juvenile xanthogranuloma; non-juvenile xanthogranuloma; non-Langerhans cell histiocytosis; bone

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Introduction

The accessory cells of the immune system consist of specialized dendritic cells (antigen-presenting) and various monocyte-macrophage (histiocytic) cell types (antigen-processing cells). The neoplastic and systemic proliferation of these accessory cell types is particularly rare;[1] additionally, until recently, because clonal markers were lacking, differentiation between a reactive and a neoplastic type of proliferation was difficult to establish.[1] Accumulation and infiltration of variable numbers of monocytes, macrophages and dendritic cells in the affected tissues is associated with a group of diverse disorders named 'histiocytoses'.[2,3]

Langerhans cell histiocytosis (LCH) is the main representative of the diseases of accessory cells characterized by the typical Langerhans cells.[4,5] Non-Langerhans cell histiocytosis (N-LCH) summarizes a group of rare diseases with different clinical presentations, pathogenesis and morphology. These include primary cutaneous N-LCH, cutaneous N-LCH with systemic involvement and primary extracutaneous systemic forms with occasional cutaneous involvement.[2-5] The location and extent of these histiocytic lesions substantially affects the course of the disease and the patient's prognosis.[1-5] Therefore, decisions regarding treatments are usually based on the extent of the disease and evidence of critical organ (risk organ) dysfunction. Risk organs for LCH include the lungs, liver, spleen and bone marrow, while risk organs for N-LCH include the skin, liver, kidneys and lungs.

Classifications

As with other rare diseases, the nomenclature for histiocytic disorders and their classification is complex and continually

evolving as a result of increasingly sophisticated phenotypic, genotypic and functional analyses.[2-6] The World Health Organization (WHO) has proposed the following classification for histiocytic disorders:[4,5]

1) Class I including LCH;
2) Class II including histiocytosis of mononuclear phagocytes other than Langerhans cells, familial and reactive haemophagocytic lymphohistiocytosis (HLH), sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease (RDD), juvenile xanthogranuloma (JXG), and reticulohistiocytoma; and
3) Class III including malignant histiocytic disorders, acute monocytic leukaemia (FAB M5), malignant histiocytosis and true histiocytic lymphoma.

The Histiocyte Society has proposed the following classification for histiocytic disorders:[6]

1) Class I (dendritic cell histiocytosis) including LCH, secondary dendritic cell processes, JXG and related disorders (Erdheim-Chester disease (ECD)), and solitary histiocytomas of various dendritic cell phenotypes;
2) Class II (non-dendritic cell histiocytosis) including primary haemophagocytic lymphohistiocytosis (familial haemophagocytic lymphohistiocytosis), secondary haemophagocytic lymphohistiocytosis (infection or malignancy associated), RDD (sinus histiocytosis with massive lymphadenopathy) and solitary histiocytoma with macrophage phenotype; and
3) Class III (malignant histiocytosis) including monocyte-related leukaemias (monocytic leukaemia M5A and M5B, acute myelomonocytic leukaemias M4, chronic myelomonocytic leukaemias), extramedullary monocytic tumour or sarcoma, dendritic cell-related histiocytic sarcoma and macrophage-related histiocytic sarcoma.

A commonly used, simple classification schema[2,3] based also on the current clinical terms classifies histiocytoses into:

1) LCH: single-organ involvement, multi-organ disease with pulmonary involvement, multi-organ disease without pulmonary involvement and multi-organ histiocytic disorder;
2) N-LCH: juvenile and non-juvenile xanthogranuloma family (JXG and N-JXG, respectively);
3) Haemophagocytic lymphohistiocytoses: familial and secondary (reactive); and
4) Histiocyte lineage-related malignancies: leukaemias (acute and chronic myelomonocytic and monocytic), and monocytic and histiocytic sarcomas. Based on this classification, the JXG family of N-LCH consists of the juvenile xanthogranuloma (cutaneous), xanthoma disseminatum (cutaneous and systemic) and ECD (systemic), and the N-JXG family consists of the solitary reticulohistiocytoma (cutaneous), multicentric reticulohistiocytosis (cutaneous and systemic) and RDD (systemic).

Revised classifications for histiocytic disorders have been proposed by Emile et al and the histiocyte group[7] and Swerdlow et al.[8] The former authors proposed a revised grouping of the $>$ 100 subtypes of histiocytoses into five groups based on their clinical and/or molecular relevance.[7] These groups have been named by the authors as follows:

1) Group L (Langerhans group including LCH, ECD and JXG);
2) Group C (cutaneous and mucocutaneous histiocytoses group including xanthogranuloma and N-JXG family of histiocytoses),
3) Group R (RDD and miscellaneous noncutaneous, N-LCH), group M (malignant histiocytoses including primary tumours and secondary tumours occurring after or sometimes simultaneously with another haematologic neoplasm); and
4) Group H (haemophagocytic lymphohistiocytosis and macrophage activation syndrome).[7]

The latter authors proposed a revision of the previous WHO classification of the lymphoid, histiocytic and dendritic neoplasms.[8] In the revised version, the classification of the histiocytic and dendritic cell neoplasms is similar to the previous except that the order of the entities is minimally altered and ECD has been added, as it should be distinguished from other members of the JXG. Histiocytic and dendritic cell neoplasms are grouped together based on the functional properties of their normal counterpart (i.e. phagocytosis and/or processing and presentation of antigens) rather than their cell of origin. Although most arise from a common myeloid precursor, a few are of mesenchymal origin (i.e. follicular dendritic cell sarcoma and fibroblastic reticular cell tumour). Moreover, the V-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation has been reported in the setting of LCH, histiocytic sarcoma, disseminated JXG, ECD and even follicular dendritic cell sarcoma.[8]

This article will discuss the clinicopathological manifestations, diagnosis and treatment of the N-LCH group, with emphasis on ECD, a clonal disorder from the JXG family, and RDD, a reactive proliferative entity from the N-JXG family.

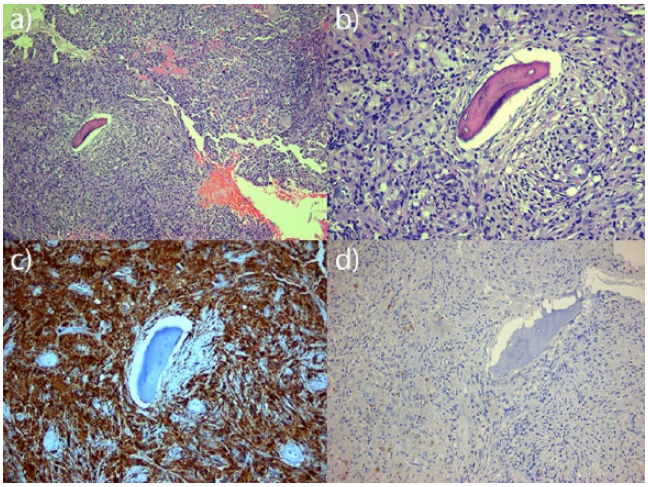

Fig. 1 Histopathological findings of ECD. Bone tissue sections show intense fibrohistiocytic infiltrate (a) with prominent proliferation of foamy histiocytes (b). Immunohistochemistry shows immunopositivity of the infiltrate for CD68 (c) but not for S100 (d). (a: haematoxylin and eosin (H&E) stain, 100× magnification; b: H&E stain, 200× magnification; c, d: 200× magnification).

Juvenile xanthogranuloma, xanthoma disseminatum, solitary reticulohistiocytoma and multicentric reticulohistiocytosis

Juvenile xanthogranuloma is a mostly cutaneous disorder, which presents at birth or during infancy. Lesions may be solitary or appear in multiple crops and they resolve with age spontaneously. The disease is occasionally found in conjunction with neurofibromatosis type 1 and juvenile myelomonocytic leukaemia. Xanthoma disseminatum is a disease of young adult males with brownish red papules and, characteristically, systemic involvement of the mucous membranes of the oropharynx, eyes and transient diabetes insipidus. The disease resolves spontaneously as well, but in aggressive cases, chemotherapeutic agents may be required in order to prevent significant morbidity before regression occurs.[2] Solitary reticulohistiocytoma is a benign N-LCH lesion that usually resolves spontaneously but may require surgical excision when local problems are present. Multicentric reticulohistiocytosis is a rare, aggressive systemic form of the disease, which characteristically presents with arthritis, cutaneous papules and nodules, and mucosal lesions. It usually arises in middle-aged women of whom over half present with arthritis. The disease may be self-limiting, especially in the rare childhood cases, or progress to a disabling and deforming polyarthritis. Steroids and methotrexate or cyclophosphamide, and infliximab in refractory cases, have been proposed for the management of the disease, with no evidence showing any particular beneficial therapeutic modality whatsoever.[2]

Erdheim-Chester disease

ECD is a rare N-LCH that was initially described by William Chester and Jakob Erdheim in 1930.[9] It accounts for up to 600 cases to date, which primarily affects male patients between their fifth and seventh decade of life;[10,11] sporadic paediatric cases have also been reported.[12] It has been described as a macrophage disorder, but has abnormal cells that are indistinguishable from those found in other members of the JXG family.[2]

Pathogenesis

The pathophysiology of ECD seems to be associated with a systemic derangement of cytokine and chemokine networks.[13-17] Elevated levels of IL-6 and IFN-a have been found in untreated patients, while IL-1 and IFN-g levels were found to be high in patients treated with IFN-a.[16] Recent data showed that BRAF V600E gain-of-function mutations are present in half of the reported cases.[14,15] The BRAF V600E mutation, which has been detected in patients with LCH,[6] has been also identified in patients with ECD, but not in patients with other N-LCHs.[15]

Pathology

A biopsy is usually obtained from bone, skin, retro-orbital or retroperitoneal soft tissue.[12,19] Positivity for CD1a and S100 raises clinical suspicion for LCH, while a lipid-laden histiocytic foamy infiltrate that immunochemically does not express CD1a and S100 guides the diagnosis for ECD (Fig. 1). The T6 protein, so-called Langerhans cells antigen, is not expressed in ECD, and CD68, a histiocyte marker, is present in both histiocytic conditions.[3] The histiocytes in ECD are also positive for CD163 and Factor XIIIa, and negative for Langerin.[20] The N-LCHs do not present Birbeck granules and they are usually accompanied by a microscopic environment including polymorphic granulomae, fibrosis, xanthogranulomatosis, proliferating fibroblasts, lymphocytic aggregates and Touton giant cells.[12]

Clinical manifestations

Diverse organs are often affected; therefore, the presentation may vary from an indolent focal disease to a life-threatening organ failure with a variety of clinical symptoms depending on the extent and distribution of the disease.[3,12,14] Skeletal involvement is almost universal (up to 96% of patients), with 50% of remaining patients expected to experience bone pain over the course of the disease (Fig. 2).[21] The most common presentation includes diffuse sclerotic lesions of the bones (with foamy

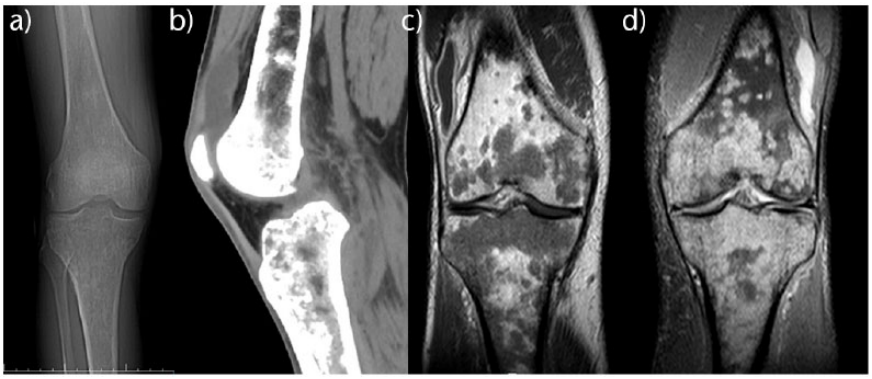

Fig. 2 Radiograph of the right knee (a) and sagittal CT scan of the left knee (b) show diffuse heterogeneity of the bones around the knee with mixed osteolytic and sclerotic areas. T1-weighted MRI of the right knee (c) and T2-weighted MRI of the left knee (d) show symmetrical bone marrow heterogeneous signal intensity without lysis of the cortex and bone deformity in a patient with ECD.

lipid-laden histiocytes on biopsy), which present especially on the diaphysis of long bones of the lower extremities, sparing mostly the epiphyses.[3] The most frequently affected bones are the femur, tibia and fibula, and less frequently the ulna, radius and humerus; the axial skeleton and epiphyseal regions are usually spared. Bone pain usually manifests around the knees and ankles.[12] Typical imaging findings include symmetrical diaphyseal osteosclerosis in radiographs and symmetrical uptake in the long bones of the extremities in bone scintigraphy.[14] Occasionally, mixed sclerotic and lytic lesions may be observed, complicating the diagnosis.[12]

The second most commonly involved system is the cardiovascular (up to 77% of patients).[14] Peri-arterial infiltration usually has little clinical significance except in the case of renovascular infiltration, which may cause systemic hypertension. Pericardial fibrosis causing tamponade, 'pseudo-tumour' of the right side of the heart, valvular infiltration occasionally requiring valve replacement, peri-coronary artery infiltration that may cause potentially fatal myocardial infarction, and fibrous encasement of the aorta ('coated aorta') have been reported.[3,14] A baseline echocardiogram may be considered in these patients and, if abnormal, an early cardiology consultation and cardiac magnetic resonance imaging may be performed to rule out cardiac involvement, which is an important cause of ECD-related morbidity and mortality.[3] Cardiac involvement appears to be significantly higher in older patients.[10]

Progression of ECD to the central nervous system (CNS) and adjacent structures can manifest a wide range of symptoms (Fig. 3a, b). Approximately 51% of ECD patients may present with CNS involvement; CNS lesions are directly responsible for 29% of all deaths.[22] Symptoms such as neurological deficits or severe disability, and clinical manifestations such as panhypopituitarism, papilloedema, diabetes insipidus, gaze disturbances, cerebellar syndromes, headache, seizures, psychiatric manifestations, paroxysmal dystonia, focal mass lesions-related radiculopathy or intramedullary spinal cord masses depend on the location, size and nature of the CNS lesions.[10,12,14,20,23,24] Diabetes insipidus, secondary to hypothalamic or pituitary infiltration, is a typical manifestation of ECD that may lead to other endocrinal abnormalities such as hyperprolactinaemia or gonadotropin insufficiency.[14]

Pulmonary involvement is also common (20% to 53% of patients); patients can be asymptomatic or experience dyspnoea, cough or chest discomfort.[20,22,25] Pulmonary involvement does not appear to be an independent predictor of worse prognosis for ECD patients.[14] Orbital involvement also occurs (up to 25% of patients) and xanthelasmas of the eyelids or the peri-orbital spaces (up to 18% of patients) are often bilateral. Orbital involvement manifests as exopthalmos due to retro-orbital infiltration, and often is resistant to treatment and requires surgical debulking.[14,20] Renal involvement (11% to 30% of patients) consists of obstructive uropathy due to retroperitoneal fibrosis or renal histiocytic infiltration. Symptoms commonly include abdominal pain, dysuria, possible development of hydronephrosis and chronic renal failure from peri-renal or ureteral obstruction (29% to 59% of patients) and nephrovascular hypertension.[14,20]

Cutaneous manifestations (27% to 30% of patients) include xanthoma like papules and peri-orbital xanthelasma like skin lesions;[10,12,20] skin involvement is described mostly in older patients.[10] Gastrointestinal tract, testes, thyroid, adrenals, skeletal muscle and breast involvement have been reported sporadically.[12,14] Systemic symptoms are present in $>$ 20% of patients; fever, weight loss, weakness and fatigue may persist in a relapsing-remitting fashion, accompanying new manifestations of the disease; however, they rarely represent a prominent complaint.[20,26]

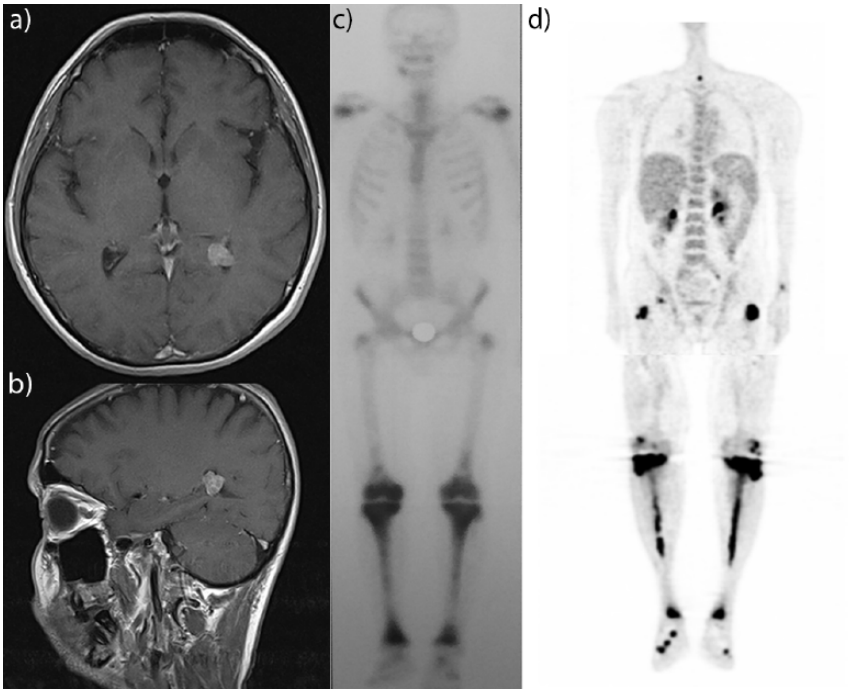

Fig. 3 Axial (a) and sagittal (b) T1-weighted MRI of the brain showing a soft-tissue lesion at the choroid plexus of the left lateral cerebral ventricle in a patient with ECD. Bone scan (c) and PET-CT (d) show symmetrically increased uptake at the humeral heads, greater trochanters, knees, tibias and small bones of the feet in a patient with ECD.

Diagnosis

As clinical manifestations of ECD lack adequate specificity, establishing a diagnosis is challenging.[20] Typical imaging findings include symmetric diaphyseal and metaphyseal osteosclerosis of the long bones, cortical thickening, coarsened trabeculae, medullary sclerosis and loss of the corticomedullary differentiation; lytic lesions may be seen in 5% to 8% of patients.[27] Bone scintigraphy and positron emission tomography (PET) exhibit symmetrically increased radionuclide uptake by the long bones of the lower extremities (Fig. 3c, d).[20] Retroperitoneal, peri-aortic ('coated aorta') and peri-renal ('hairy kidney') involvement can be observed on both contrast-enhanced and unenhanced CT scans,[12] while MRI shows replacement of the normal fatty marrow.[27]

A correct diagnosis of ECD is obtained by tissue sampling and histological identification of pathological histiocytes in the appropriate clinical and radiological context.[20,28] Multiple samples may be required to confirm the diagnosis, especially in the case of bone biopsies, since the decalcification process could make the material less appropriate for mutational analysis.[20,28] A baseline evaluation with CT scans of the chest, abdomen and pelvis, PET scan, MRI of the brain and heart is recommended in all patients to classify ECD according to organ system dominance, as this influences the clinical outcome and therapeutic options.[20,28]

Treatment

The scarcity of patients with ECD renders the implementation of controlled randomized trials impossible. Consequently, no therapies have been approved for ECD; current treatments are based on an anecdotal evidence base and retrospective data.[3,12] In a recent systematic review,[10] authors studied 331 manuscripts describing 448 patients with ECD. The authors concluded that the efficacy of all treatment modalities remains undefined, due to the frequent concomitant administration of more than one drug and short follow-up.

Interferone-α (IFN-α) is the first-line treatment, providing the best management strategy with sustainable stabilization of the disease in most cases.[12] Response to IFN-α is also regarded as the only major treatment predictor of survival, in particular in patients with CNS involvement.[10] The efficacy is variable according to the site involved. The recommended dosage ranges from 3 000 000 units three times per week to 9 000 000 units three times per week for patients with extensive disease with CNS and cardiovascular involvement.[12,14,20] Common side effects of IFN-α therapy include gastrointestinal symptoms, depression, alopecia, myelosuppression and systemic symptoms such as fever, fatigue, myalgias and arthralgias.[20] Pegylated forms of IFN-α are generally more tolerated and are administered at dosages in the range of 135 to 200 μg per week.[12,14,22]

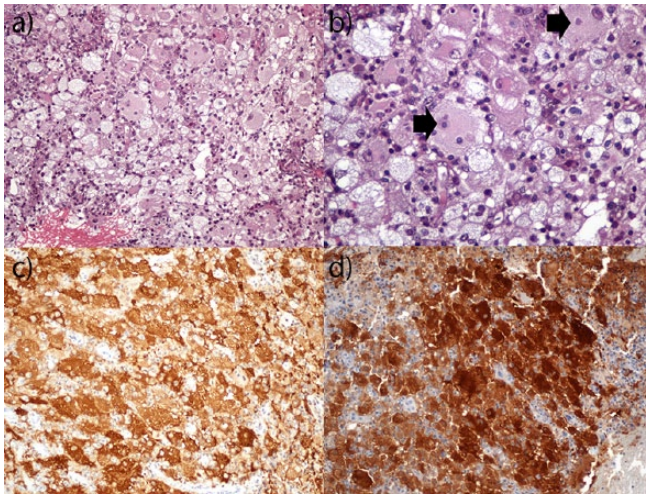

Fig. 4 Histopathological findings of RDD. Bone tissue sections show aggregates of large histiocytes and mononuclear inflammatory cells (a), the former showing emperipolesis (arrows) (b). S100 (c) and CD68 (d) immunostaining shows strong immunopositivity of the histiocytes for both markers. (a: H&E stain, 100× magnification; b: H&E stain, 200× magnification; c, d: 200× magnification).

Other treatment options for ECD include recombinant human interleukin-1 receptor antagonist (anakinra, 1 to 2 mg/kg/day), cladribine, tyrosine kinase inhibitors, anti-TNFα monoclonal antibody (infliximab) and autologous haematopoietic stem cell transplantation.[3,14,20] Corticosteroids, vinblastine, vincristine, cyclosphosphamide, doxorubicin, cyclosporine and radiation therapy have also been used.[14] However, corticosteroids had a very limited impact on the disease; various chemotherapeutic agents used provided eventually only temporary relief.[12] Some patients may benefit from surgical debulking, particularly those with severe and resectable intracranial or retro-orbital lesions; however, lesions tend to re-grow rapidly.[12,20] Radiation therapy fails to yield a sustainable clinical response and bisphosphonates exhibit only partial success in the management of osseous involvement.[12] After the discovery of BRAF V600E mutation in histiocytes in a significant proportion of ECD patients, the BRAF inhibitor vemurafenib has been used in the treatment of ECD patients who harboured the specific mutation, and exhibited promising results with a rather impressive efficacy.[13,29] These results provide an exciting means of targeted approach in treating severe BRAF-mutated forms of ECD refractory to first-line treatments, and open new perspectives for newer BRAF inhibitors with better safety profiles.[14,20]

Prognosis

The prognosis of patients with ECD is variable and depends on the extent of the disease and of organ involvement.[14] Currently available therapeutic options have improved the prognosis of ECD patients,[20] with reported one-year and five-year survival rates at 96% to 68%, respectively. CNS involvement has been found to be an independent predictor of fatal outcome, while treatment with IFN-α and pegylated IFN-α has been an important independent predictor of survival.[22]

Rosai-Dorfman disease

RDD, also known as sinus histiocytosis with massive lymphadenopathy, was originally described by Destombes in 1965,[30] but it was recognized as a distinct clinical entity by Rosai and Dorfman in 1969.[31] It is a rare idiopathic histiolymphoproliferative disorder that is generally characterized by peripheral, bilateral, painless and massive cervical lymphadenopathy.[7,30-33] Mediastinal, inguinal and retroperitoneal nodes, and extranodal sites such as the skin and soft tissue, CNS, orbit, upper respiratory tract, gastrointestinal tract and bones may also be involved.[32]

Pathogenesis

RDD has histological features that have been well characterized;[31,33] however, the aetiology remains unknown, and existing theories attribute the pathogenesis of this rare entity to an idiopathic autoimmune process and/or an infectious factor.[32,33] Although RDD has been reported in patients with immunoglobulin (Ig) G4-related disease, no clear evidence suggests that these disorders share a common pathogenesis.[7,33-35] It has been postulated that immune dysfunction and viral infections, such as human herpesvirus (HHV), parvovirus B19 and Epstein-Barr virus (EBV) may play a role in the pathogenesis of RDD.[32,36-39] Finally, more implications about the origin of the disease have been made after reports of patients who developed RDD after bone marrow transplant for precursor-B acute lymphoblastic leukaemia,[40] and concurrently or after Hodgkin's and non-Hodgkin's lymphoma.[41]

Pathology

In the setting of RDD, the involved lymph nodes are enlarged and matted with thickened capsules. Histologically, the normal lymph node architecture is altered by pericapsular fibrosis and dilated sinuses that are heavily infiltrated with histiocytes, lymphocytes and plasma cells.[42] Histiocytes may be abundant or sparse, with round or oval, vesicular nuclei and abundant pale pink to foamy cytoplasm scattered within a dense background of inflammatory cells.[43] The hallmark of this disease, and the key to diagnosis, is emperipolesis (lymphocytophagocytosis: histiocytes containing lymphocytes, plasma cells, neutrophils and erythrocytes) (Fig. 4a, b).[31,32] The presence of the engulfment of lymphocytes and erythrocytes by histiocytes that express S-100 is considered diagnostic of RDD. Histiocytes also present positive staining for

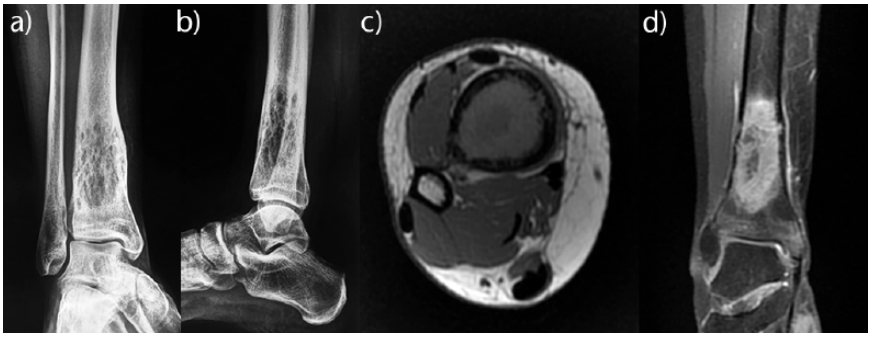

Fig. 5 Anteroposterior (a) and lateral (b) radiographs of the right distal tibia and ankle show a distal tibia mixed osteolytic lesion with cortical expansion. Bone biopsy showed RDD. Axial T1-weighted (c) and coronal T2-weighted (d) MRI shows a marrow-replacing infiltrative lesion at the distal tibia with cortical scalloping. The lesion shows low signal intensity on T1-weighted sequences and high signal intensity on T2-weighted sequences.

α1-anti-chymotrypsin, CD1a and CD68 antigens (Fig. 4c, d).[44] RDD lesions have a moderate expression of IL-6 that could be related to the associated polyclonal plasmacytosis and hypergammaglobulinaemia. Furthermore, the lesions tend to express IL-1β and TNF-α. Systemic symptoms in RDD may be related to the enhanced production of these cytokines.[45]

Clinical manifestations

Patients of any age can be affected; however, RDD is most commonly seen in children and young adults (mean age of onset, 20.6 years), with a slight predilection for males (58%) and individuals of African descent.[32] Approximately 87% of the patients initially present with cervical lymphadenopathy ('bull neck')[46] accompanied by fever, night sweat, malaise and weight loss. Laboratory examination often shows elevated erythrocyte sedimentation rate (ESR), anaemia, neutrophilia and polyclonal hypergammaglobulinaemia.[32] Extranodal involvement by RDD was initially thought to be uncommon, but some reports suggest that it may be present in up to 40% of cases.[32,35] The most common extranodal sites of involvement are the skin and soft tissue, CNS, eye and orbit, bones, upper respiratory tract and salivary glands. Rare reported sites of involvement include the male and female genital tract and breast.[32]

The skeletal system is involved in approximately 5% of patients with extranodal RDD. Extra-osseous manifestations usually co-exist in these cases, while primary solitary osseous involvement is very uncommon.[32,47] Apart from being primarily involved, skeletal involvement may occur secondarily to the extension from adjacent soft-tissue lesions.[48,49] RDD of bone is characterized by gradual swelling of the region and occasional pain and tenderness.[50] Although any bone may be affected, the long bones, skull and spine have been the most common.[51] Lesions in the long bones may be located in the metaphyses, diaphysis or epiphyses (Fig. 5a, b),[49] and multiple lesions may exist in the same bone or multiple bones may be involved.[49,50]

Diagnosis

The differential diagnosis of extranodal RDD of the bone is occasionally difficult, because clinical signs and symptoms are non-specific, and the disease is rare.[52] Radiographically, skeletal lesions of RDD are typically osteolytic and intramedullary.[32] On MRI, RDD typically appears as a marrow-replacing, infiltrative process in the trabecular space that is iso-intense or hypo-intense to muscle on T1-weighted sequences, and markedly hyper-intense on fluid-sensitive sequences (Fig. 5c, d).[43] Fludeoxyglucose F-18 PET scan was found to be a sensitive indicator for early prediction of treatment response in patients with systemic RDD.[53] Biopsy is required to confirm the diagnosis; emperipolesis is considered to be the hallmark of the disease.[31,32,54-58] Occasionally, RDD of bone may be histologically misdiagnosed as chronic osteomyelitis or lymphoma because of its extensive inflammatory component.[58]

Treatment

Treatment for RDD is advised only in patients who are symptomatic or have vital organ or system involvement.[59] Surgical debulking and radiation therapy should be performed in the presence of life-threatening manifestations.[59] Radiation therapy alone has been proven effective in some patients whose symptoms persist or recur after surgical intervention, and for those patients with inoperable lesions.[60] In patients with RDD requiring systemic treatment, steroids are a first-line therapeutic option that produces responses in both classical and extranodal disease. Chemotherapy has been also used with varying degrees of success.[59,61]

The treatment of choice for symptomatic bone lesions is intralesional excision (curettage) with satisfactory local control and pain relief.[58,62,63] After curettage, the bone defect can be left as is or packed with acrylic bone cement or bone

graft as bone void fillers.[58] Radiation therapy, chemotherapy and long-term corticosteroid therapy have also been reported for the management of disseminated or unresectable bone disease as second-line treatments.[59,60,64]

Prognosis

The clinical course is variable, with alternating episodes of worsening and relief of symptoms. However, the outcome is usually good, with spontaneous regression of the disease. If lesions are not massive and do not involve vital organs the patient should only be observed. In the course, RDD is usually self-limiting and eventually recedes, making systemic therapy rarely required.[7]

Conclusions

ECD and RDD N-LCH are rare disorders which are challenging to diagnose with multi-organ involvement and systemic symptoms, and they respond to therapy in an unpredictable way. The key to successful therapy is accurate identification at tissue level and appropriate staging. Patients should be observed and monitored in a long-term pattern. Prognosis depends on the extent of the disease and the extent of organ involvement; it is generally good for RDD and variable for ECD.

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