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Review Article

The "Rare" or "Non-LCH" Histiocytic Disorders in Childhood: A Brief Overview

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ABSTRACT

Diseases of the monocyte, macrophage and dendritic cell system are referred to as histiocytoses. Based on improved understanding of their pathobiology and molecular background histiocytoses have been recently re-classified into five groups. Nevertheless, for practical reasons the histiocytoses are grouped into: Langerhans cell histiocytosis (the most common entity), hemophagocytic lymphohistiocytosis (encompassing primary and secondary hyperinflammatory syndromes), non-Langerhans cell histiocytoses (encompassing entities and syndromes not belonging to one of the first two categories), and true histiocytic malignancies. Proliferation of bone marrow-derived mature histiocytes with CD68+/CD163+/CD1a-/CD207- phenotype is the common denominator of the non-Langerhans cell histiocytoses (non-LCH). The clinical manifestations are extremely heterogeneous, though partially overlapping. There are some distinct disease forms (particularly those belonging to the juvenile xanthogranuloma family) confined to the skin. Some other entities may present as systemic diseases requiring differential diagnosis with hematopoietic malignancies and solid tumors. This paper provides a brief overview on key clinical features, diagnostic criteria, and management of the most common systemic non-LCH entities: Juvenile Xanthogranuloma (JXG), Rosai-Dorfman disease (RDD), and Erdheim-Chester disease (ECD).

The non-LCH histiocytoses with systemic manifestation are uncommon diseases in the pediatric hematology/oncology praxis. Due to their broad spectrum of manifestations, keeping in mind their key features and an adequate index of suspicion are important for timely and correct diagnosis. Non-LCH histiocytoses have to be considered in the differential diagnosis of papulonodular cutaneous lesions with xanthomatous appearance, osteolytic and osteosclerotic lesions with benign morphology and histiocytic infiltration, orbital lesions with proptosis, suprasellar masses presenting with central diabetes insipidus, as well as leptomeningeal mass lesions.

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Introduction

Diseases, in which monocytes, tissue macrophages (histiocytes) and dendritic cells, as well as their bone marrow precursors play a dominant role, are referred to as histiocytoses. The histiocytoses are currently divided into 5 large groups. Relevant from a pediatric hematological point of view are the groups L (Langerhans cell histiocytosis - LCH, Erdheim-Chester disease – ECD, and systemic juvenile xanthogranuloma - JXG), R (Rosai-Dorfman disease - RDD and other systemic non-LCH syndromes), and H (hemophagocytic lymphohistiocytoses HLH).[1]

Rare histiocytoses, also called Non-Langerhans cell histiocytoses (non-LCH), include all proliferative disorders of histiocytes, macrophages and dendritic cells that are

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not classified as Langerhans cell histiocytosis (LCH) and do not belong to the hemophagocytic lymphohistiocytosis (HLH) group of diseases.[2] The non-LCH are very rare in childhood. Their classification is challenging due to extreme diversity of clinical manifestations, extent and prognosis. Furthermore, aside of overlapping clinical manifestations, the non-LCH share common histology, cellular immunophenotype, molecular mechanisms and causative mutations.[1, 3]

In 2005 Weitzman & Jaffe proposed a pragmatic classification of the rare histiocytoses into three groups: primarily cutaneous histiocytoses (i.e. cutaneous juvenile xanthogranuloma family, reticulohistiocytoma, and cutaneous Rosai-Dorfman disease); cutaneous histiocytoses with major systemic component (xanthoma disseminatum and multicentric reticulohistiocytosis); and mainly systemic histiocytoses with or without cutaneous involvement (ECD, systemic JXG, and systemic RDD). [4] This overview will focus on systemic non-LCH.

Juvenile Xanthogranuloma (JXG)

Epidemiology

JXG is a disease of early childhood (median age at presentation 2 years), but it can be present at birth or manifest in school age. JXG is the most common non-LCH disorder with an estimated incidence of one case per million. However, the disease may be underreported, particularly those cases presenting with solitary cutaneous lesions, which account for 80-90% of all cases.[5, 6] Males are more frequently affected, particularly among patients with multiple cutaneous lesions and those with systemic disease. There is an association between JXG, neurofibromatosis type 1 (NF1), and juvenile myelomonocytic leukemia (JMML). Patients with JXG and NF1 have a 20-32-fold risk of JMML compared to those with NF1 only.[7]

Pathology

The pathogenesis of JXG is still not fully understood. Based on the immune phenotype of the lesional cells (CD14+, CD68+, CD163+, FXIIIa+, CD1a- and CD207-), JXG should be categorized as a macrophage-related histiocytosis, but the evidence of ERK activation and rare cases of co-existing LCH and JXG lesions suggest relation to dendritic cell progenitors. Typical JXG lesions have benign appearance and reveal accumulations of histiocytic cells that are morphologically very similar to Langerhans cells. Frequently, so-called Touton giant cells are found in variable numbers.

The histiocytic cells may have a partially foamy, vacuolated cytoplasm. In some of the lesions, also a spindle cell cytology is found. The lesions are mostly localized in the dermal connective tissue. Immunohistochemistry is essential for a reliable differentiation from other histiocytic proliferations, particularly LCH.

Clinical Manifestations

Cutaneous JXG can present as single or multiple brown to yellow papules or nodules, predominantly localized on the face, head, and neck, followed by upper trunk and the extremities. It can present at any site, including the nails, eyelid, lips, palms and soles, penis and clitoris. During infancy, JXG more commonly presents as multiple, ranging from few to hundred lesions. Cutaneous JXG usually has a benign course, but the spontaneous involution of the lesions can take months to years.

Systemic JXG accounts for 4% of all cases and is typically seen in very young children (median age 3 months). Its diagnosis could be quite challenging, as about half of the cases do not have cutaneous manifestations. The most common presentation is a solitary mass in the deeper soft tissues, followed by liver, spleen, lung, ocular and brain involvement.[6, 8] Several organs and sites can be affected in different combinations and, therefore, careful laboratory and imaging work-up has to be performed in all patients, including those with apparently localized cutaneous disease. Marrow involvement can manifest with unexplained cytopenia.[9] Pulmonary lesions are solid nodules of varying size on imaging, and in the experience of the author may be clinically silent.[9] Liver disease can manifest with hepatomegaly and signs of organ dysfunction.[10]

There are some extra-cutaneous manifestations either as an isolated finding or in the setting of a systemic disease. Timely recognition of these lesions is important to prevent irreversible complications (e.g. intraocular and cerebral JXG).

Intraocular JXG occurs in 1% of the children with cutaneous JXG, mostly in infants.[6] It can present as a visible scleral nodule or red eye, glaucoma, hyphema, retina or optic nerve involvement and may result in complete loss of vision despite receiving treatment.[11]

JXG affecting central nervous system is estimated to account for 1.2 % of all cases.[6] Depending on the location, it can manifest clinically with increased intracranial pressure, seizures, polyuria and polydipsia, blindness, or developmental delay. On MRI, single or multiple leptomeningeal lesions can be identified which are not characteristic for JXG, and thus in the absence of cutaneous manifestation, the diagnosis can be confirmed only after a biopsy.

The intracranial JXG lesions are typically homogenous lesions with isointense appearance on T1- and T2-weighted images and enhancement after gadolinium administration.

Diagnosis

Typical cutaneous lesions can be reliably diagnosed without biopsy by an experienced physician. However, in some cases differential diagnosis with dermatofibroma, mastocytosis and other histiocytic disorders can be difficult. Biopsy is mandatory for extra-cutaneous JXG due to uncharacteristic appearance of the lesions. Systemic and extra-cutaneous lesions of JXG are indistinguishable from ECD in many cases. Therefore, besides histopathological and immunohistochemical findings, the final diagnosis has to consider the clinical pattern of organ involvement and the imaging findings. Some experts consider extracutaneous JXG and ECD a continuum of the same disease.[1, 8] In case of positive testing for BRAF, NRAS, KRAS, or MAP2K1 gain-

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of-function mutations, the disease is classified as ECD.[1]

Management

The majority of the patients with cutaneous JXG present with a favorable course and prognosis and do not need to receive any treatment. However, extensive diagnostic work-up is needed to exclude systemic disease, particularly in patients below the age of 2 years. For children <4 years with concurrent JXG and NF1, frequent follow-up visits including CBC are mandated because of the increased risk for developing JMML.[8] Likewise, structured ophthalmological follow-up (every 3-6 months until age of two years) is recommended for younger children due to the increased risk for ocular involvement.[8] Ocular involvement requires treatment in an experienced ophthalmology center.

Surgery can be sufficient as a treatment option for solitary, symptomatic extra-cutaneous lesions (including intracerebral). For unresectable lesions and systemic disease, treatment with the standard regimen used in LCH (prednisolone + vinblastine) is effective in most cases.[12] Clofarabine seems to be another effective drug for non-LCH, including JXG.[13]

Rosai-Dorfman Disease (RDD)

Synonyms include: sinus histiocytosis with massive lymphadenopathy (SHML); Rosai-Dorfman-Destombes disease (RDD); Faisalabad syndrome and H syndrome.

RDD is a non-LCH characterized by benign proliferation of S-100 positive histiocytes within the sinus of the lymph nodes and lymphatic vessels of internal organs.[14]

Epidemiology

Due to lack of population-based studies, the exact incidence of RDD is unknown. The most reliable source of information about this disease is the RDD registry founded by J. Rosai.[14] The estimated incidence of RDD is probably less than 10 % of the incidence of LCH.[14] RDD can manifest at any age from birth until elderly, with a median age of 20 years at presentation. It is most frequently diagnosed in children and young adults. The male: female ratio is 1.4: 1. A familial form of RDD has been later recognized to occur in patients with underlying Faisalabad, H syndrome or autoimmune lymphoproliferative syndromes (ALPS).[8]

Pathogenesis and Histopathology

The etiology and pathogenesis of RDD remains still uncovered. The fact that characteristic RDD histopathology has been documented in patients with familial syndromes or other malignancies, suggests that it is a heterogeneous syndrome with common morphology, rather than a single entity. Indeed, J. Haroche and O. Abla proposed a classification encompassing all clinical forms of RDD.[8] Based on the clinical observations, it is believed that RDD is the result of an aberrant immune regulation with cytokine-mediated monocyte migration and activation. In contrast to LCH and ECD, BRAF mutations have not been found in RDD, yet.[3, 15] Other mutations (KRAS, MAP2K1, NRAS, and ARAF) have been identified in less than 50% of the studied cases.

The hallmark of RDD is proliferation of a characteristic subpopulation of macrophages with signs of emperipolesis (red blood cells, lymphocytes and plasma cell are engulfed by activated histiocytes) in lymph node sinusoids. The sinusoids are expanded due to accumulation of pale stained histiocytes in combination with a variety of polyclonal plasma cells. Histiocytes are positive for CD14, CD68, CD163, and S-100, but negative for CD1a and CD207 on immunostaining. Another characteristic feature of RDD is thickened and fibrotic lymph node capsule.

The microscopic picture of extranodal foci of RDD is similar to that observed in the lymph nodes. It is remarkable to see structures similar to pathologically altered lymph nodes in organs such as kidneys and brain. However, there are some differences in the morphology of nodal and extranodal foci. In general, the extranodal foci are characterized by more pronounced fibrosis, less pronounced accumulation of histiocytes and less pronounced emperipolesis compared with affected lymph nodes. The fibrotic stroma contains more expressed vessels and plasma cells located along the vessels. As with Hodgkin's lymphoma, diagnostic criteria for extranodal lesions are less strict if the patient has documented lymph node involvement.[14]

Clinical Manifestations

RDD most frequently presents with a massive bilateral, painless cervical lymphadenopathy with constitutional symptoms (e.g. fever, night sweats, and weight loss), a typical picture, which has given the name SHML of the classical nodal disease. Only lymph nodes were affected in 239 of 423 patients in the international registry.[14] In 97% of all patients with RDD, the presence of bilateral (symmetrical or asymmetric) cervical lymphadenopathy was noted at various stages of the disease, which in typical cases is the leading manifestation of the disease. All groups of cervical lymph nodes can be affected, each group separately or in different combinations. At the onset of the disease, the lymph nodes are mobile and single, but often merge into large multinodular conglomerates during the course of the disease. In some patients, these conglomerates reach enormous sizes causing neck deformation. The remaining groups of lymph nodes, including axillary, inguinal and intrathoracic are affected in 80 % of the cases.

Analysis of "RDD registry" showed that the disease occurs in the extranodal sites in 43% of the cases, which are sometimes the only disease manifestation. The most frequent localizations of extranodal lesions according to the international registry: skin, soft tissue, upper respiratory tract, bone, eye, retroorbital tissue and the brain. The clinical manifestation of extranodal disease is nonspecific. The diagnosis is established usually after a biopsy.

Skin lesions in RDD are the most frequent extranodal localization, but they are rarely isolated. They present in the form of multiple papules and nodules. Half of the patients recover independent of the treatment, but the skin lesions can also persist or recur for a long time.

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Skeletal lesions in RDD are osteolytic in nature. Lesions of different sizes with uneven contours without periosteal reaction are localized more often in tubular bones. Multifocal osteomyelitis, LCH, and bone metastases of neuroblastoma, particularly in patients without severe lymphadenopathy should be considered in differential diagnosis.[16]

One of the most frequent extranodal localizations is involvement of the cavities and paranasal sinuses in the form of polyps or tumor-like masses. RDD can affect the orbit, eyelids and the eyeball.[17] Orbital damage is often accompanied by proptosis, which requires differential diagnosis with LCH, neuroblastoma and rhabdomyosarcoma. RDD can also affect suprasellar structures and cause diabetes insipidus and loss of function of the anterior pituitary, which are indistinguishable from LCH.

Although rare, RDD can present with isolated CNS lesions. Intracranial disease presents as meningioma and usually occurs without extracranial lymphadenopathy.[8, 18]

Frequent, but nonspecific laboratory findings are normochromic normocytic or hypochromic microcytic anemia, elevated ESR and serum immune globulins.[14]

Diagnosis

Diagnosis of RDD requires histopathological examination with immunohistochemistry.[8] Once the diagnosis has been confirmed, a structured work-up is needed to rule out associated autoimmune disease and to document all involved sites.[8]

Differential diagnosis depends on disease presentation. The classical nodal SHML requires work-up for infection-related lymphadenopathy, as well as exclusion of Hodgkin and non-Hodgkin lymphoma. The extranodal RDD is usually diagnosed by histopathological findings of biopsy performed for other suspected diseases (e.g. meningioma in case of cerebral RDD).

Clinical Course and Prognosis

The clinical course of RDD is hardly predictable. Observation of spontaneous regression in some cases and the fact that many patients have lost contact after diagnosis, indicate a non-aggressive course in most cases.[14] The lack of a staging system and of a uniform patient assessment does not allow identifying reliable prognostic factors. Nevertheless, associated immunological disorders as well as multiple extranodal lesions seem to have unfavorable impact on prognosis. Lesions of kidneys, lower respiratory tract and liver also have adverse effects on disease prognosis.

Treatment

There are no systematic data on the efficacy of treatment of RDD. Patients presenting with nodal disease only and without associated autoimmune disease tend to have higher chances for spontaneous regression. For such patients "wait and watch" approach is justified. Therapy is needed in patients with associated diseases and those with extranodal RDD, particularly for those with involvement of vital organs. Surgical debulking may be helpful in patients with intracranial disease or with obstruction of the upper airways. Radiation therapy has been successfully used for orbital disease impeding visual compromise.[19] Systemic corticosteroids stop the fever, but their effect on the dynamics of the size of the lymph nodes is not well proven. Various combinations of steroids, vinblastine, methotrexate, mercaptopurine and alkylating agents have been used without consistent effect.[20-23] According to the scarce data available, it seems that the most effective combinations in the past were steroids, vinca alkaloids and alkylating agents. Imatinib, cladribin and clofarabine were effective in cases of refractory or recurrent RDD.[13, 24] In patients with associated autoimmune disease, particularly ALPS, rituximab and sirolimus may be effective.

Erdheim-Chester Disease (ECD) or Lipoid Granulomatosis

ECD is a non-LCH, characterized by infiltration of the involved tissues by foamy CD68+CD1a- histiocytes.[25]

Epidemiology

The incidence of ECD is unknown. Less than 1000 cases have been reported since the first description in 1930.[25] The disease usually presents in adults aged 40-60 with a male predominance. It is very uncommon in childhood with less than 15 pediatric cases reported to date.[8] Interestingly, among the reported pediatric cases, girls were more frequently affected.[26]

Pathology

ECD has been considered for decades to be a reactive disorder due to aberrant immunity. The recent discovery that it is a clonal disease due to constitutive activation of the MAPK pathway completely changed the view on its pathobiology. It is now classified as an inflammatory myeloid neoplasm.[25] BRAF mutations have been documented in 57-75% of the cases in larger cohorts, which is similar to the mutation frequency observed in LCH.[3, 25]

The histological appearance can vary considerably depending on the location and evolution phase of the lesions.[27] An overarching feature is the proliferation of mature histiocytes in a background of inflammatory stroma. However, the histiocyte content can vary considerably in reverse proportion to the tissue fibrosis. Characteristic foamy histiocytes are not always present. Moreover, the histiocytes in ECD share common immune phenotypes with the other non-LCH disease revealing positive staining for CD68, CD163, FXIIIa, and fascin. Therefore, compatible histopathology is obligatory for the diagnosis of ECD; however, the final diagnosis has to be corroborated by molecular studies and by the pattern of clinical manifestations and imaging findings.[28]

Clinical Manifestations

ECD is a systemic disease and can affect virtually all organs. Constitutional symptoms include fever, weakness and weight loss. Patients may present with skeletal, pulmonary, retroperitoneal, endocrine, neurologic, skin,

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renal, and cardiovascular involvement.[28] The extent and distribution of the disease determine the clinical course and prognosis.[8, 28] The disease spectrum varies from asymptomatic skeletal lesions to multisystemic involvement with life-threatening complications.

Involvement of the long bones is seen in almost all (>90%) patients. It characteristically presents as a symmetric bilateral osteosclerotic lesion of distal lower limbs with metadiaphyseal location. The bone lesions can present with mild to moderate pain, but may be asymptomatic. Orbital infiltration occurs in about 25% of the patients. It is more often bilateral with orbital masses causing more or less prominent proptosis, and less frequently oculomotor nerve palsy or optic nerve compression. Xanthelasma of the eyelids are encountered also in about 25% of the ECD patients. Skin lesions located elsewhere can present as scaly plaques or papulonodular lesions with xanthomatous appearance. Pituitary gland infiltration leads to diabetes insipidus in about 25% of the patients and in some cases is accompanied by hyperprolactinemia and gonadotropin insufficiency. Orbital and pituitary involvement are seen in both LCH and JXG, and their differential diagnosis based on clinical findings only is difficult.

Distinct feature of ECD compared to other histiocytic disorders is its predilection for cardiovascular system. It is encountered in 70% of the patients and requires rigorous imaging work-up as the lesions can be clinically silent. The most frequent finding on CT or MRI (40-50%) is a circumferential sheathing of the aorta, described as "coated aorta". The periaortic infiltration may extend to other main arteries (e.g. renal arteries) and cause complications, such as renovascular hypertension. Pericarditis is another serious cardiovascular manifestation, documented in about 30% of the patients. Pseudotumoral infiltration of the right atrium has also been reported.

The lung can be also involved and radiologically presents with interstitial opacification. Advanced pulmonary lesions are associated with extensive fibrosis that may lead to cardiorespiratory failure.[29]

Retroperitoneal infiltrates mimicking retroperitoneal fibrosis are another characteristic feature of ECD observed in about 50-70% of the patients. The radiologic findings on CT or MRI are described as "hairy kidney". The retroperitoneal ECD can result in unilateral or bilateral hydronephrosis. Central nervous system involvement can cause cerebellar and pyramidal symptoms and manifestations such as headache, seizure, cognitive impairment, cranial nerve palsy and sensory disturbance.

Prognosis

ECD has a variable prognosis but it is overall poorer in those with CNS involvement. Before IFN-alpha, mean survival after diagnosis was 19.2 months. Nowadays, with IFN-alpha treatments, the mortality rate is only 26%, and 5-year survival is 68%. The introduction of the very effective targeted BRAF inhibitor vemurafenib promises further improvement of the patient fate.

Diagnosis

Diagnosis of ECD is based on histopathologic findings within the appropriate clinical and radiological context.[8, 28] The hallmark of histological finding is xanthogranulomatous or xanthomatous infiltration of tissues with foamy histiocytes, which stain positive for CD68, CD163, FXIIIa and negative for CD1a and CD207. Bone x-rays usually display bilateral and symmetric cortical osteosclerosis of the long bones, while technetium 99m bone scintigraphy shows almost constantly evidence of symmetric and abnormally strong labeling of the distal ends of the long bones of the lower limbs. Abdominal CT scan may reveal a ''hairy kidney'' appearance (in 50-70%) and/or "coated aorta" (40-50%), findings highly suggestive for ECD. Recommendations for the baseline clinical evaluation of patients with ECD are available in the consensus guidelines elaborated by an international panel of experts.[28]

Differential Diagnosis

Due to the multisystemic character of the disease and innumerable manifestations related to ECD, the list of differential diagnoses is very long, depending of involved systems and location of the lesions. The most common differentials to be considered include LCH, RDD, Takayasu arteritis, Wegener's granulomatosis, primary hypophysitis, chronic recurrent multifocal osteomyelitis, malignancies, neurosarcoidosis, mycobacterial infections and metabolic disorders.

Management and Treatment

Therapy is recommended at diagnosis in all patients, except for those patients with minimally symptomatic disease.[28] Standard or pegylated IFN-alpha is considered as first line treatment for all forms of ECD. Higher doses (9 million units, 3 times per week) are required on a long-term basis for those with CNS and cardiac localizations. Bisphosphonates can alleviate bone pain. Cladribine can be effective in those with orbital involvement that have been resistant to other forms of treatment.

Discovery of recurrent mutations of the MAPK pathway (particularly BRAFV600E) in the majority of the ECD patients opened an opportunity for a targeted therapy. The first report on vemurafenib used to treat adult patients with concomitant ECD and LCH showed dramatic response.[30] This observation has been subsequently validated by a larger patient cohort and in addition it has been shown that sustained remissions are possible with continuous treatment.[31] Recently published results of a basket trial corroborate the previous reports and suggest vemurafenib as the new standard treatment for ECD patients positive for BRAFV600E.[32] Indeed, vemurafenib has been recently approved for this indication by FDA.[33]

Conclusion

Non-LCH, particularly those with systemic manifestation are uncommon diseases in the praxis of pediatric hematology/oncology. As a result, keeping in mind their key features and an adequate index of suspicion are important for timely and correct diagnosis. Non-LCH have to be considered in the differential diagnosis of papulonodular cutaneous lesions with xanthomatous

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appearance, osteolytic and osteosclerotic lesions with histiocytic infiltration, orbital lesions with proptosis, suprasellar masses presenting with central diabetes insipidus and leptomeningeal mass lesions.

Conflict of Interest: None declared.

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