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Reticulohistiocytoses: a revision of the full spectrum.

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Bulleted Statement:

What's already known about this topic?

Reticulohistiocytoses are rare dermatological disorders characterized by prototypical histological features and highly variable clinical pictures. Although most of literature focuses only on the multicentric reticulohistiocytosis, we contributed to highlight the presence of different clinical subsets of patients, as well as the importance of the detection of molecular alterations in the prognostic and therapeutic managements of these patients and in line of what observed in other histiocytic disorders.

What does this study add?

We reviewed the literature and tried to redefine the whole clinical spectrum of reticulohistiocytosis, in accordance to the clinical sub-classification of histiocytoses. We propose a clinical sub-classification in 5 different groups and highlighted the diagnostic overlap between reticulohistiocytoses with different clinical and prognostic features, as well as with other histiocytoses. Finally, we reviewed the molecular landscape of reticulohistiocytoses and discussed their clinical and therapeutic management.

ABSTRACT

Reticulohistiocytoses (RH) are rare and clinically heterogeneous histiocytic disorders of dermatological interest. Three clinical entities with superimposable histopathological features are currently considered, namely: solitary reticulohistiocytoma, diffuse/generalized reticulohistiocytosis and multicentric reticulohistiocytosis. Although in the last decade RH studies have only minimally

progressed, histiocytosis research has advanced considerably: the prognostic and therapeutic importance of the clinical sub-classification of histiocytosis patients as well as of the detection of genetic alterations in the genes of the ERK pathway has been highlighted. According to these insights, we previously reported the presence of molecular alteration RH and described a subset of patients with disseminated multisystem involvement lacking arthritis. In the present review, we aim to update and revise the knowledge regarding RH. We first reviewed their histopathological, immunophenotypical and ultrastructural features, discussed their histopathological differential diagnosis with other conditions characterized by infiltrates made of oncocytic or epithelioid cells (with special regard to Destombes-Rosai-Dorfman Disease (DRDD)) and finally summarized the molecular landscape of RH. We therefore tried to adjust the clinical sub-classification of Langerhans cell histiocytosis to the clinical phenotypes of RH, outlining 5 clinically different groups of patients. Finally, we reconsidered the clinical workflow to the evaluation of RH patients, in light of the 5 different clinical groups and discussed the different therapeutic approaches and the possible role of target inhibitors.

Keywords:

Non-Langerhans cell histiocytosis; histiocytoses; mononuclear-phagocyte system; multicentric reticulohistiocytosis; myeloid neoplasia; cutaneous lesions; myelomonocytic leukemia; Destombes-Rosai-Dorfman disease; Erdheim-Chester disease.

LIST OF ABBREVIATIONS

AHN: associated with hematological neoplasm

ECD: Erdheim-Chester disease

NLCH: non-Langerhans cell histiocytosis

MIFT: microphtalmia transcription factor

MS: multisystem

MPS: mononuclear-phagocyte system

MR: multicentric reticulohistiocytosis

LCH: Langerhans cell histiocytosis

DRDD: Destombes-Rosai-Dorfman disease

RH: reticulohistiocytosis/es

SSmf: single system multifocal

SSsf: single system single-focal

INTRODUCTION

Reticulohistiocytoses (RH) are a group of extraordinarily rare and clinically heterogeneous proliferative disorders of the Mononuclear-Phagocyte System (MPS), predominantly affecting the skin and characterized by unique histopathological features.[1-2] They were first described by Targett in 1897 as "Giant-celled tumors of the integuments".[3] Later, in 1982, Goette et.al.[4] included three different entities in the group, namely "diffuse cutaneous reticulohistiocytosis", "reticulohistiocytoma" and "multicentric reticulohistiocytosis" (MR) based on the original descriptions by Montgomery and O'Leary[5], Zak[6] and Goltz and Laymon[7] respectively. These three disorders have been variably recognized in the literature. Currently, although in the 2016 revisedclassification of histiocytoses by the Histiocyte Society only MR and (solitary) reticulohistiocytoma are included within the "C(utaneous)-group"[8], the 2018 WHO classification of skin tumors describes all three entities in a specific chapter.[1]

In the last two years, new clinical variants of RH have been described and the genetic landscape of these disorders has been finally revealed.[9-11] Therefore, considering the current clinical heterogeneity of RH and the possible clinical impact of the new insights in RH biology, we hereby propose a revision of RH to (re)define the clinical boundaries of these rare disorders and to review their diagnostic and therapeutic management.

HISTOPATHOLOGY AND MOLECULAR BIOLOGY

"Reticulohistiocytosis" is primarily a histopathological category and therefore its diagnosis relies on the analysis of biopsy specimens.[1-2,12-13] Otherwise, the definition of each RH clinical variants is based on the evaluation of the full clinical-pathological picture. In some cases, (e.g. MR) months of follow up are needed to gather enough findings to refine the diagnosis. Therefore, the pathologist should better release a diagnosis of "reticulohistiocytosis" without further specifications whereas the clinician should complete it at a later time.

Histological and immunohistochemical findings

Histopathological findings are the same for the whole RH-group and all the involved tissues (Figure 1).[1] Cutaneous lesions show well-circumscribed mid- to deep-dermal infiltrates, sparing epidermis, upper-dermis and skin appendages, thus resulting in the presence of a Grenz zone. The epidermis may be flattened with hyper- or parakeratosis. The infiltrate is composed by large epithelioid mononuclear or binucleated cells with round to kidney-shaped nuclei and one or more prominent nucleoli. The cytosol has a finely-granular eosinophilic appearance, resembling ground-glass. Mature lesions may include giant mono-, bi- or multi-nucleated cells with randomly oriented nuclei and ground-glass cytoplasm. Foamy-, Touton- and Langhans-cells are absent or very rare. RH cells are surrounded by a variable number of small lymphocytes (mostly CD8+) and few granulocytes. Plasma cells are virtually absent. A reduction of the inflammatory infiltrate and the presence of dermal fibrosis may be observed in old regressing lesions.[1, 11-13,] Giant cells may display emperipolesis of neutrophils or lymphocytes.[9] Lesions involving other tissues such as synovia, gastrointestinal mucosa, pleura or bone-marrow show identical features with a lower number of giant cells.[14] In MR, fragmentation and phagocytosis of collagen (collagenophagocytosis) are reported in some cases.[15]

RH-cells stain for periodic acid-Schiff, acid phosphatase and non-specific esterase, scarlet red O and Baker's acid hematein.[16] Immunohistochemically, they are positive for CD4, CD11b, CD14, CD45/LCA,

CD68/KP1, CD68/PGM1, CD163 and vimentin, stain variably for CD33, factor XIIIa, S100 protein, fascin and lysozyme and are negative for CD1a, CD34 and CD207/langerin.[17-21] Recently, the positivity for Microphtalmia transcription factor (MIFT)[22], CD10[23] and CD141/thrombomodulin[2] has also been reported.

Electron microscopy

RH-cells display ultrastructural features of activated mononuclear "antigen processing" cells. The nuclei show prominent nucleoli, granular euchromatin and a peripheral dense band of heterochromatin. Golgi complexes, rough endoplasmic reticulum, mitochondria, lysosomes and phagosomes are very numerous. Coated vesicles and myelin bodies are variably present, but no Birbeck granules or large amounts of lipid vacuoles are observed.[24] Pleomorphic cytoplasmic inclusions and collagenophagocytosis are seen in up to 20% of RH-cells. Pleomorphic cytoplasmic inclusions are complex membrane structures surrounding electron-dense areas, granules or vesicles, found in progressive nodular histiocytosis and RH only. Collagenophagocytic activity is an ultrastructural hallmark of MR.[15] Collagen fibers may be seen in phagosome as well as free within the cytoplasm. Plasma membrane may show peripheral villi, similarly to osteoclast cells.[24]

Histopathological differential diagnosis

From a histopathological point of view, the differential diagnosis of RH includes other histiocytoses as well as disorders with infiltrates made of epithelioid oncocytic cells[25] or epithelioid macrophages including sarcoidosis[26], Spitz nevus[27], histiocytic sarcoma[28], epithelioid fibrous histiocytoma[29] and giant-cell tumors of bone.[30] Immunophenotype together with architectural features, background, atypia and clinical data are generally enough to differentiate all of these disorders from RH (Table 1).

Regarding the differential diagnosis between RH and other histiocytoses, the first step is the exclusion of dendric-cell-derived disorders through immunophenotyping (e.g. CD1a, CD207, CD123 or CD303), whereas the second step regards the differentiation of NLCH entities and the study of their cytological features (e.g. foamy or non-epithelioid ground-glass cells vs RH-cells). A particularly complicated differential diagnosis of RH is DRDD. DRDD is a clinically pleomorphic histiocytic disorder, characterized by infiltrates made of large to giant mono- and multinucleated macrophages with pale cytosol, admixed with a rich background of lymphocytes and especially plasma cells, often in clusters.[31-32] Although emperipolesis and S100 protein positivity are considered two distinctive features of DRDD, the former may also be observed in RH and Erdheim-Chester Disease (ECD), whereas the latter is considered to be one of the less specific MPS markers.[33] Interestingly, DRDD was previously diagnosed as a nodal condition in 95% of cases, while today it is regarded as a generally extranodal disorder, with classical (nodal) presentation accounting for only 8% of cases.[34] As a consequence, RH/DRDD overlap may be partly caused by the more diffuse knowledge of DRDD among surgical pathologists as opposed to RH (being mainly a dermatopathologically-recognized entity). Moreover, the recent description of "ECD with RDD-like lesions" further widened the diagnostic overlap between these entities and reduced the role of histopathology in the differential diagnosis of histiocytic disorders.[35]

Molecular biology of reticulohistiocytoses

In the last four years, the discovery of the molecular landscape of histiocytoses boosted the research on possible molecular drivers of the RH. In 2017 Fusco et.al. reported the case of a RH clonally related to an acute myeloid leukemia (both harboring a t(1;9)) providing for the first time evidence for a clonal origin of RH.[7] In 2019 Bonometti et.al. described the presence of the BRAFV600E mutation in a case of disseminated-RH[10], whereas Murakami and colleagues highlighted the presence of two possible driver mutations (i.e. mutations in MAP2K1 and TET2 genes) in one MR patient.[11]

Altogether these data suggest a molecular homology between RH and other histiocytoses, with MS cases potentially harboring activating mutation in the ERK pathway.[36] Moreover, in our opinion the description of MAP2K1 mutation in MR strengthens the possibility of a diagnostic overlap between RH and those MS cases of non-Langerhans cell histiocytoses (NLCH)classified as "ECD with Rosai-Dorfman-like lesions".[35]

CLINICAL FINDINGS AND SYSTEMIC ASSOCIATIONS

For all histiocytoses, the sub-classification based on the degree of spreading in Single-system (SS) and Multisystem (MS) conditions has become of great clinical and prognostic importance.[1, 37] The three traditionally recognized entities of RH cover their most frequent clinical phenotypes. Nevertheless, the literature describes cases of SS-RH sparing the skin as well as of MS cases lacking articular involvement.

To update the full clinical spectrum of RH in accordance to the principles mentioned above we hereby propose a revised sub-classification of RH that includes:

(1) "localized" SS-single focal (SSsf) conditions;

(2) "diffuse/generalized" SS-multifocal (SSmf) conditions;

(3) "disseminated" proliferative MS disorders involving multiple organs and sparing the joints;

(4) systemic inflammatory MS conditions, associated with arthritis (i.e. MR);

(5) SS or MS-RH associated with hematological neoplasms (AHN).

Such division recapitulates the pathobiology of the diverse entities within the spectrum.[37] A further clinical and epidemiological characterization is given in Table 2**.**

1. Single system-single focal reticulohistiocytosis: cutaneous and extracutaneous reticulohistiocytoma

SSsf-RH is the most commonly encountered RH in clinical practice. It manifests with solitary lesions involving a single tissue. SSsf-RH are more frequently described among young adult males. Cutaneous SSsf-RH manifest as an asymptomatic papular-nodular grey-whitish to dark-red skin lesion, ranging from 0.2 to 1.5 cm in diameter, typically located on the trunk, limbs and head and neck region (Figure 2A, B).[1,6, 20] The literature also describes cases of extracutaneous SSsf-RH involving the eye, orbit, central nervous system oral mucosa or penis.[38-42] SSsf-RH is a benign and sometimes self-healing condition that rarely recurs.[20] Dermatological differential diagnosis includes mastocytoma, early-phase of xanthogranuloma, DRDD, atypical fibroxanthoma, Spitz nevus and pyogenic granuloma. Bony localization of SSsf-RH should be differentiated from LCH (eosinophilic granuloma), DRDD and xanthogranuloma of bone.

2. Single system-multifocal reticulohistiocytosis: diffuse (generalized) cutaneous reticulohistiocytosis

SSmf-RH is a cutaneous condition characterized by a papular-nodular eruption generalized over the whole skin surface, but lacking any signs of systemic involvement. Fingers, juxta-articular and paronychial regions are regularly spared.[1-2, 5, 43-47] Exceptional cases may display clinical pictures akin to Xanthoma Disseminatum, but they still lack MS involvement and show typical RH histopathology.[48] No radiological or laboratory abnormalities are reported in these patients. Due to their high similarity, SSmf-RH is frequently misdiagnosed as “MR lacking arthritis” and should also be differentiated from generalized eruptive histiocytosis and from RH-AHN because of their similar dermatological phenotype.[49]

3. Multisystem non-arthropathic reticulohistiocytosis: disseminated reticulohistiocytosis

We previously described four cases of MS-RH sparing the joints[10] and a further (and prior) description is given by Zurac et.al.[50] Disseminated-RH presents in young adults with a cutaneous papular eruption, slowly merging into large reddish plaques (Figure 3A-C). Bone involvements, diabetes insipidus and organomegaly may occur (Figure 3D). Disseminated RH has a chronic progressive behavior. Acute evolution may develop after decades, eventually leading to death. The overall clinical and biological picture of disseminated-RH is similar to other MS-histiocytoses such as Disseminated Juvenile Xanthogranuloma, Xanthoma Disseminatum and ECD.[8, 10] Nevertheless, ECD involves the skin more frequently as xanthelasmata. One of our cases of disseminated-RH harbored a $BRAF^{V600E}$ mutation.[10] Disseminated RH should be carefully differentiated from MR and especially from RH-AHN, whoe prognosis and clinical management are different. Interestingly, disseminated-RH may largely overlap with the previously mentioned "ECD with Rosai-Dorfman-like lesions" that frequently harbor MAP2K1 mutations.[35]

4. Multisystem arthropathic reticulohistiocytosis: the "multicentric reticulohistiocytosis"

MR is the most frequently described form of RH. It is a systemic inflammatory condition predominantly affecting adult females and invariably involving the skin together with the joints.[1] Often the first symptom is the development of an erosive arthritis (up to 70% of cases). The most frequently involved joints include: distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints, wrists and knees. Shoulders, elbows and ankles are also involved in around 25% of patients. Joint stiffness and swelling of soft tissues are commonly associated. Articular lesions in MR are symmetrical, destructive and progressive as in other inflammatory arthritides (arthritis mutilans) but they lack periarticular osteoporosis, interphalangeal ankylosis, osteophytes formation or periosteal osteodeposition. Therefore, radiography plays an important role in the diagnosis of MR. The skin lesions may appear up to 3 years after the articular involvement: they

consist of a slowing appearing acral (e.g. distal limbs, head and neck), yellowish to brown-reddish papular-nodular eruption. Skin lesions involving the fingers typically occur above joints (juxtarticular, Figure 3D-E) or nail-folds (paronychial coral bead-like lesions) (Figure 3F). Multiple nodules may merge into a bumpy cobblestone-like mass.[51-54] Up to 50% of the patients displays involvement of the mucosa of the upper respiratory tract. Pulmonary, pleural, cardiac and salivary gland involvement has been reported anecdotally.[54-56] Other signs and symptoms include: weight loss, pruritus, fever, weakness, dysphagia and myalgia. Abnormal laboratory findings include anemia, hyperlipidemia (30-50% of patients) and elevation of erythrocyte sedimentation rate and C-reactive protein (50% of cases).[56-57]

It is important to take into account that MR often associate with neoplastic and autoimmune disorders. Up to a third of patients develops malignancy synchronously or metachronously with MR. Most of these cancers are of epithelial origin.[57-60] Moreover, in some cases, remission from cancer lead to concurrent remission of MR.[61] For this reason, it is also described as a paraneoplastic condition. Autoimmunity is frequently associated in MR and the two disorders may overlap (e.g. Sjögren's syndrome, systemic lupus erythematosus, dermatomyositis).[62] Serology and radiology may help to differentiate the findings. Finally, MR shows clnical similarities to François syndrome (dermochondrocorneal dystrophy), the latter being a very rare paediatric inherited disorder characterized by nodular juxtarticular eruption, osteochondral deformities and corneal opacities. Histological and epidemiological data are sufficient to differentiate the two disorders.[63]

5. Reticulohistiocytosis associated to hematological neoplasm (RH-AHN)

RH other-than-MR are reported to associate almost exclusively with hematological neoplasms (RH-AHN) in line with what recently highlighted for other histiocytoses.[64] In the international medical literature, fourteen cases of RH-AHN are described between 1976 and 2018: [65] twelve associated to myeloid neoplasms (including acute and chronic conditions)[4,9,66-76] and two more with

lymphoproliferative disorders.[77-78] All described patients are adult males who display a generalized papular eruption before, concurrently or shortly after the diagnosis of the underline malignancy (Figure 3G). Symptomatic or asymptomatic cytopenia and organomegaly are often the first sign of the neoplasia. Sometimes RH cells may be found in the bone marrow together with the malignant cells. Other symptoms, such as fatigue, dyspnea or fever, largely depend on the hematological neoplasm.[65] RH-AHN is frequently misdiagnosed as generalized eruptive histiocytosis due to a descriptive use of such diagnostic category.[66, 70, 73-74, 76] Moreover, RH-AHN should also be differentiated from other cutaneous manifestations in course of myeloid malignancy, especially in patients diagnosed with chronic myelomonocytic leukemia.[79]

EVALUATION AND MANAGEMENT

Given the extended spectrum of RH, it seems necessary to outline a workflow for the management of RH patients (Figure 4, Table 2)**.** Once the histopathological diagnosis of RH has been established, the patients should undergo a full clinical examination, including: complete blood count, blood chemistry and radiological investigation of bones and abdominal organs. SS-RH of skin, mucosae or bones should be followed up by dermatologists, orthopedists or other specialists, according to the involved organ. A curative surgical approach can be adopted in SSsf cases[20], whereas corticosteroids, methotrexate, IFN-alpha or PUVA-based regimens may be established for SSmf cases.[2, 46] Periodic examinations are suggested to rule out possible systemic involvement or leukemic evolution.[9] RH patients developing arthritis should be examined by a rheumatologist to rule out MR. If the diagnosis of MR is confirmed, treatment with corticosteroids, methotrexate, NSAID or IFN-alpha should be instituted./span>[53] In such cases, the clinician needs also to investigate a possible paraneoplastic etiology (epithelial neoplasms) and consequently treat the patient according to the underlying neoplastic condition. Patients with MS disease without arthropathy should be followed up by a team of internists and multiple specialists. Therapeutic protocols developed for other MS histiocytoses such as ECD or DRDD are the best available choice today. Whenever a targetable genetic alteration is detected, a treatment with specific inhibitors should be considered.[11] Blood tests should be repeated periodically, whereas bone marrow biopsy should be reserved to those patients presenting long-lasting cytopenia and/or leukocytosis.[65] Patients with complete blood count abnormalities but with negative bone marrow biopsy should be followed in line with the corresponding SS or MS-RH category.[79] In case of positive bone marrow investigation, RH-AHN patients should be followed by hematologists and treated according to the associated hematological neoplasm.

ETIOPATHOGENESIS

Little is known about the etiopathogenesis of RH. The sub-classification of RH proposed in this work would recapitulate the possible clinical biological and ethiopathological differences between the different entities, as already demonstrated for LCH.[37]

SS-RH are considered reactions to trauma, insect bite or other immune stimulations.[1] MR is best defined as a chronic inflammatory response to a systemic immune derangement (e.g. in autoimmune disorders or cancer). Various authors demonstrated high levels of proinflammatory cytokines (e.g IL-1b, IL-6, IL-8, IL-12, TNF-a and MCP-1) in both serum and involved tissues.[81] Likewise, treatment with systemic anti-inflammatory drugs as well as with TNF-inhibitors seems to be effective in improving both skin and articular lesions and in lowering serum inflammatory cytokines levels.[52-53] Disseminated RH fit with the "inflammatory myeloid neoplasm" model, akin to MS-LCH or ECD.[82] Finally, RH-AHN may represent the cutaneous manifestation of a systemic hematological myelodysplastic/myeloproliferative neoplasm.[79] Indeed, a clonal relation between RH and AHN, as well as a concurrent response to chemotherapy, has been described.[9]

CONCLUSIONS AND FUTURE DIRECTIONS

RH are a group of rare histiocytic disorders with heterogeneous clinical manifestation and different therapeutic management. The histopathological features allow to address the diagnosis of RH, but at the same time they are not enough to define a specific clinical subgroup. Therefore, the histopathological diagnosis of RH should represent a guide for the clinician to correctly complete the diagnosis that should investigate the involvement of different organs and tissues, as well as the association with rheumatological, oncological and hemato-oncological disorders. For these peculiarity, and for their wider clinical spectrum, RH should be carefully differentiated from other NLCH and treated according to the specific clinical subgroup.

Considering their sometime challenging differential diagnosis, future works should determine the degree of overlap between RH and other NLCH (especially DRDD) and establish valid differential criteria to their diagnosis. Moreover, the frequency and the pathogenicity of molecular alteration in RH (with special regard on MAP2K1 mutations) should be determined. Finally, the efficacy of target inhibitor and multi-kinase inhibitors should be evaluated in the therapeutic management of RH.

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Figure 1: Histopathological and ultrastructural features of RH. RH are characterized by diffuse upper- to mid-dermal infiltration (A) of large cells with ground-glass cytosol, one (B) or more nuclei (C) with prominent nucleoli that may show emperipolesis of the surrounding lymphocytes and neutrophils (D). RH stain positive for CD163 (E), factor XIIIa (F) and CD14 (G), and usually have a low Ki-67 proliferation index (H). Ultrastructurally, RH cell are metabolically active, and contain numerous mitochondria and lysosomes (I). MR may also display typical pleomorphic cytoplasmic inclusions (J) as well as images of collagenophagocytosis (K).

Figure 2: Dermatological presentation of SS-RH. SS-RH almost invariably involve the skin. SSsf-RH (solitary reticulohistiocytoma) presents as a reddish single firm nodule growing on the limbs (A) or trunk (B). SSmf-RH (diffuse/generalized reticulohistiocytosis) displays a papular-nodular eruption made of reddish or isochromic lesions involving the whole skin surface (C-F) lacking systemic manifestations.

Figure 3: Clinical presentation of MS-RHC and RH-AHN. MR involve the skin together with other organs and tissues. MS non-arthropathic RH (disseminated reticulohistiocytosis), display a slowly growing papular eruption merging into large plaques located on the head and neck region, the skin folds and skin areas subjected to chronic pressure (A-B). Epiphysis of long bones may be involved (C). MR involve the skin in a distinctive fashion, with nodular juxta-articular (D,E) or papular perionychial (coral-bead) lesions (F). RH-AHN, is indistinguishable from SSmf-RH, as it presents with a reddish papular-nodular skin eruption, in association with blood cell count changes or symptoms related to the underline malignancy (G).

Figure 4: Workflow to the diagnosis of the clinical sub-groups of RH. AHN: Associated to another hematologica neoplasm, CPA: cyclophosphamide, HSCT: hematopoietic stem cell transplantation, IFN: interpheron-alpha2a, JXG: Juveline Xanthogranuloma, MTX: methotrexate, RH: reticulohistiocytosis.

Table 1: Histological differential diagnosis of reticulohistiocytosis. C: cutaneous-group, M: malignant histiocytoses group, L: Langerhans cell histiocytosis group, R: Destombest-Rosai-Dorfman disease group, according to the Revised Classification of histiocytic and dendritic cell neoplasms (see reference 8).

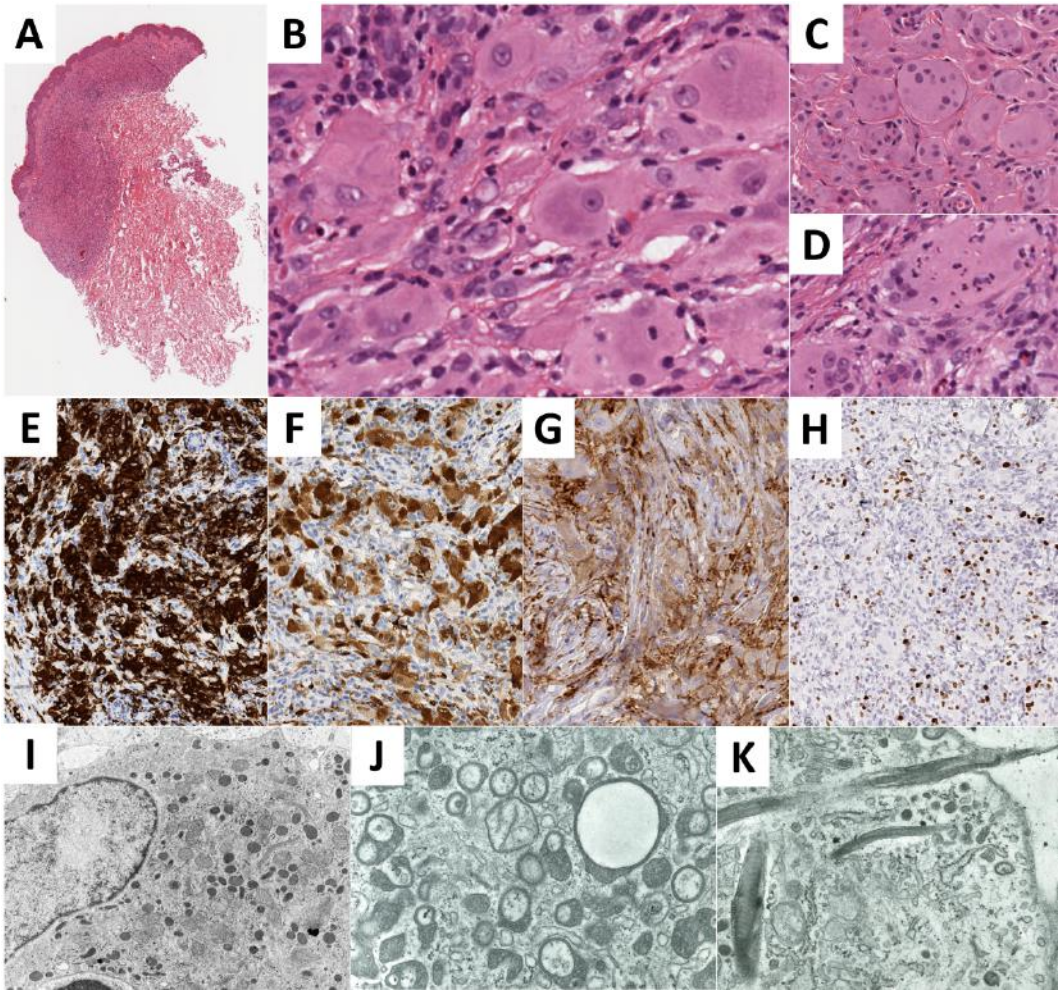
Table 2: Differential features of the reticulohistiocytosis subgroups proposed in the article. AHN: Associated with hematological neoplasm, CPA: cyclophosphamide, ECD: Erdheim-Chester disease, GEH: generalized eruptive histiocytosis, HSCT: hematopoietic stem cell transplantation, IFN: interpheron-alpha2a, JXG: Juveline xanthogranuloma, LCH: Langerhans cell histiocytosis, MR: multicentric reticulohistiocytosis, MTX: methotrexate, DRDD: Destombes-Rosai-Dorfman disease.

	Reticulohistiocytoses	Langerhans Cell Histiocytosis	Rosai-Dorfman Disease	Xanthogranuloma family	Sarcoidosis	Spitz nevus	Histiocytic sarcoma	Epithelioid fibro-histiocytoma	Giant cell tumor of bone
Group/type (see ref. 8)	C	L	R	L, C	reactive	melanocytic	M	fibro-histiocytic	fibro-histiocytic
Age group	young adults	pediatric > adults	adult	pediatric > adults	adults	pediatric	adults	adults	young adults
Location	various	various	head and neck, trunk	various	various	limbs	various	limbs, head and neck	epiphysis of long bones
Number of lesions	single or multiple	single or multiple	single or multiple	single or multiple	single or multiple	single	single or multiple	single	single
Cytology	large mono- to multinucleated epithelioid with ground-glass cytosol	large round cells with large reniform nuclei	large mono- to multinucleated macrophages with pale cytosol	foamy macrophages, Touton- and Langhans-type giant cells	epithelioid macrophages, Langhans and foreing-body giant cells	large spindled to epithelioid more or less pigmented cells	pleomorphic large cells with large eosinophilic cytosol with mild to frequent atypic figures.	medium to large sized epithelioid cells with abundant eosinophilic cytosol and vescicular nuclei	giant round to polygonal osteoclast-like multinucleated cells

Architecture	diffuse histiocytic proliferation	diffuse histiocytic proliferation	diffuse histiocytic proliferation	diffuse histiocytic proliferation	nodules of tighlty arranged cells	junctional and dermal nests; pagetoid scatter	discohesive diffuse proliferation	exophytic nodule with prominent vascularization	espansive erosive lesions with necrosis, fibrosis, aneurysmal changes and intravascular plugs
Background	lymphocytes, neutrophils	eosinophils, macrophages, lymphocytes	cluster of plasma cells, lymphocytes, neutrophils	lymphocytes, neutrophils	lymphocytes	lymphocytes, macrophages	lymphocytes, plasma cells, macrophages and eosinophils	lymphocytes	foamy macrophages
Phenotype	CD163+, CD68+, S100+/-, CD1a-, CD207-	CD1a+, CD207+, S100+, CD68-, CD163-	S100+, CD68+, CD163+/-, CD1a-, CD207-	CD163+, CD68+, S100+/-, CD1a-, CD207-	CD163+, CD68+, S100-, CD1a-, CD207-	MelanA+, S100+, HMB45+/-, CD68-, CD163-, CD1a-	CD163+, CD68+, lysozyme+, CD45RO+, CD1a-, HMB45-	ALK+, EMA+, CD30+/-, SMA-, desmin-, CD68-	CD68+, vimentin+, RANKL+, S100+/-
Referenceă	[1]	[8]	[30-31]	[8, 12]	[25]	[26]	[27]	[28]	[29]

	Single system		Multisystem		Associated with hematological neoplasms
	Single-focal	**Multifocal**	**Disseminated**	**Arthropathic (MR)**	
Median age (range)	35 (2-74)	46 (8-68)	35 (3-52)	47 (8-74)	59 (22-84)
M:F ratio	1,5:1	1:2	1,5:1	1:3	males only
Hypotesized etiology	local reactive condition	generalized reactive condition	Inflammatory myeloid neoplasm	systemic inflammatory/pareneoplastic disorder	hematological neoplasm
Medical speciality	dermatology	dermatology	multidusciplinary	rheumatology and dermatology	hematology-oncology
Prognosis	very good	very good	good	good	depending on the AHN
Skin involvement	papules and nodules (absent in extracutaneous cases)	diffuse papules and nodules	papules, nodules, plaques	papules on juxtarticular regions, head and neck	papules and nodules
Joints involvement/ arthropathy	-	-	-	+	-
Bone involvement	+ (rare and absent in cutaneous cases)	-	+ (100%)	-	+ (25%)
Diabetes insipidus	-	-	+ (60%)	-	-

Organomegaly	-	-	+ (20%)	-	+ (42%)
Blood counts	-	-	anemia	anemia	cytopenia, leukocytosis
Descibed molecular alterations (n. cases)	none	none	BRAFV600E (1)	MAP2K1, TET2 and other (1)	t(1;9) (1)
Therapy	surgical, wait-and-see	PUVA, MTX, wait-and-see	MTX, IFN, prednisone	prednisone, MTX, NSAID, CPA	chemotherapy, HSCT
Similar histiocytoses	JXG, DRDD	GEH	ECD, MS-DRDD, DRDD-like ECD	none	LCH or ECD-AHN
Number of described cases	100	30	5	350	14
Original description	Zak [6]	Montgomery and O'Leary [5]	Bonometti et.al. [10]	Golz and Laymon [7]	Goette et.al. [4]
References	[20]	[45-47]	[10, 73]	[11, 53-55]	[9, 47, 69-79]



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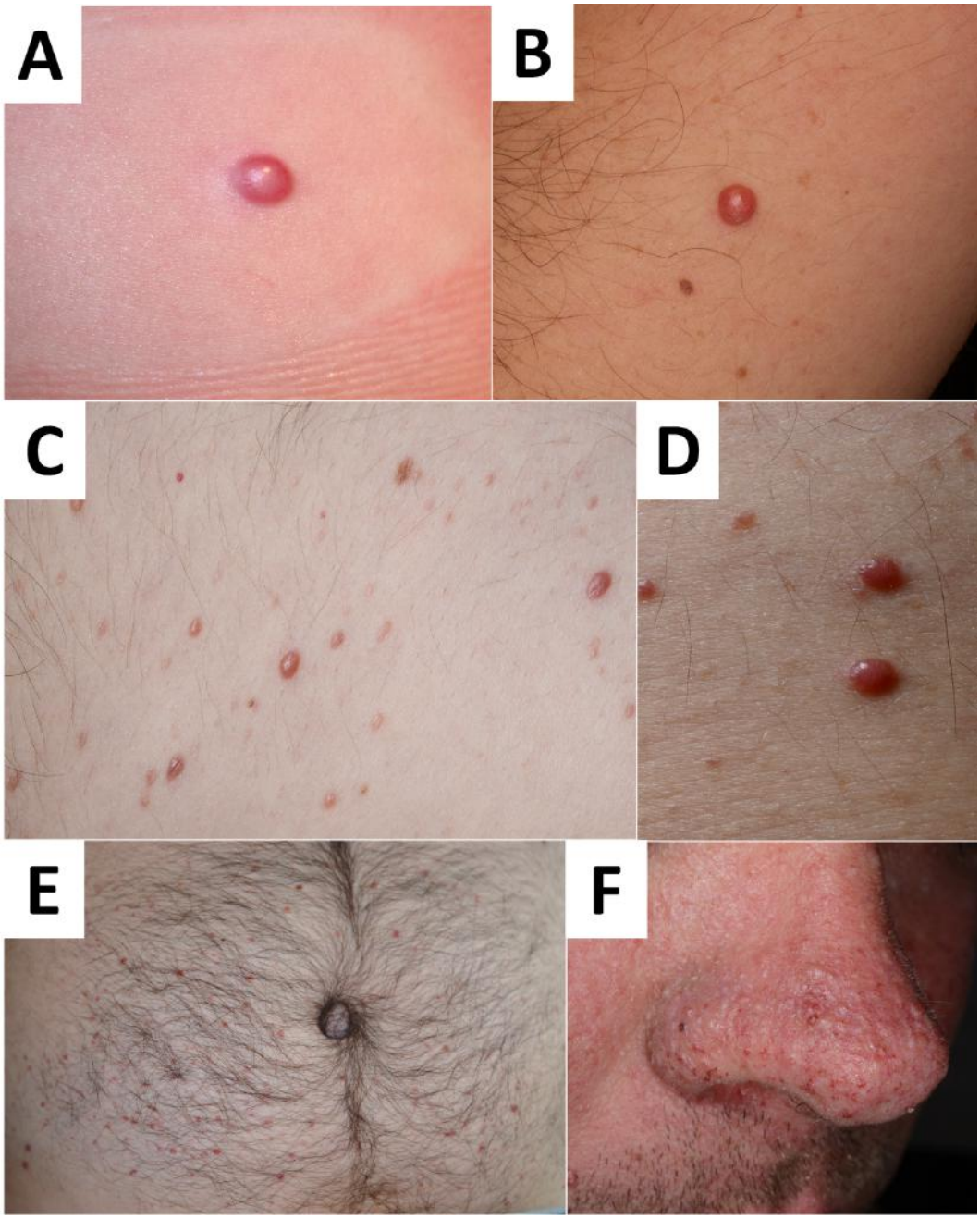

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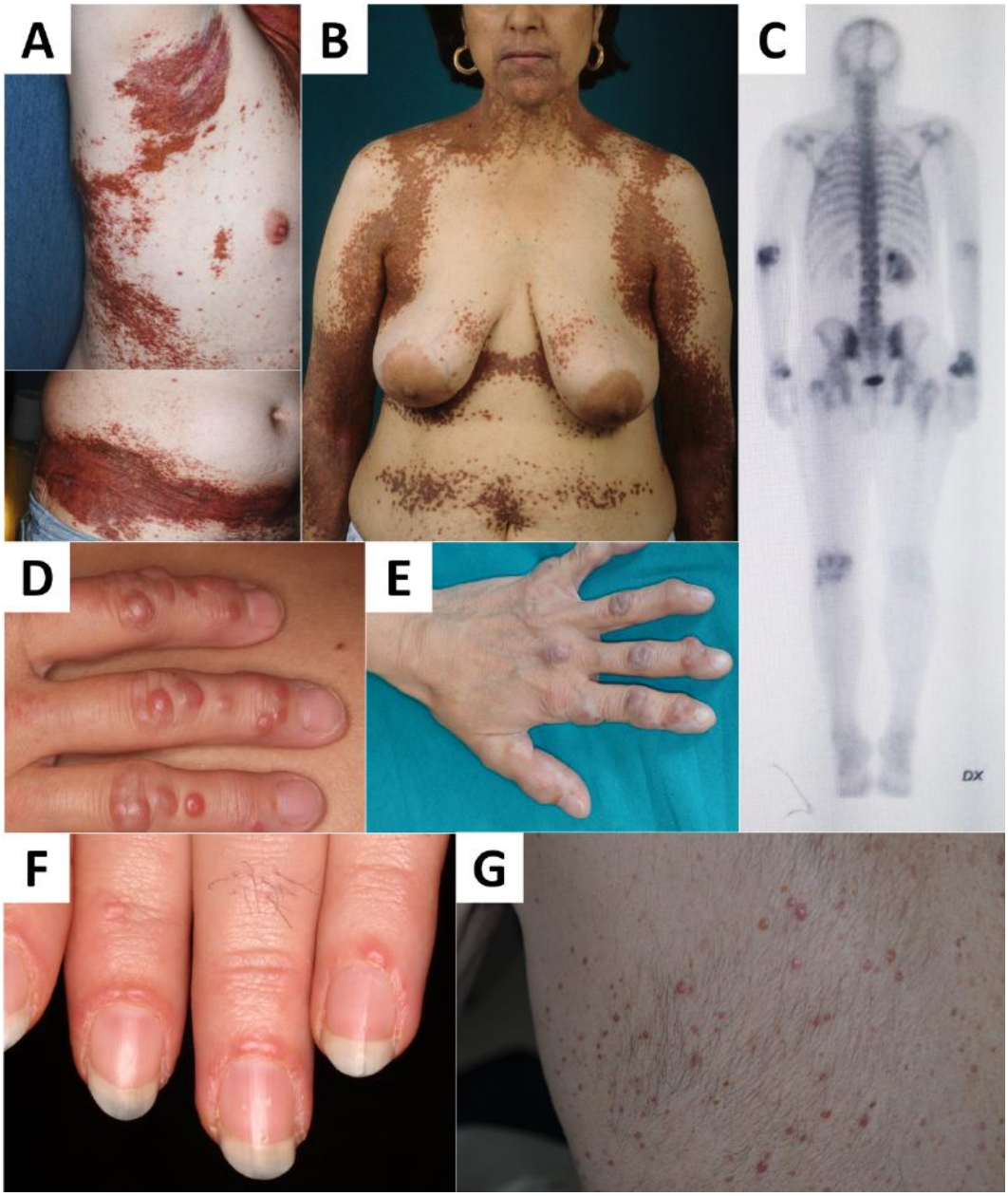

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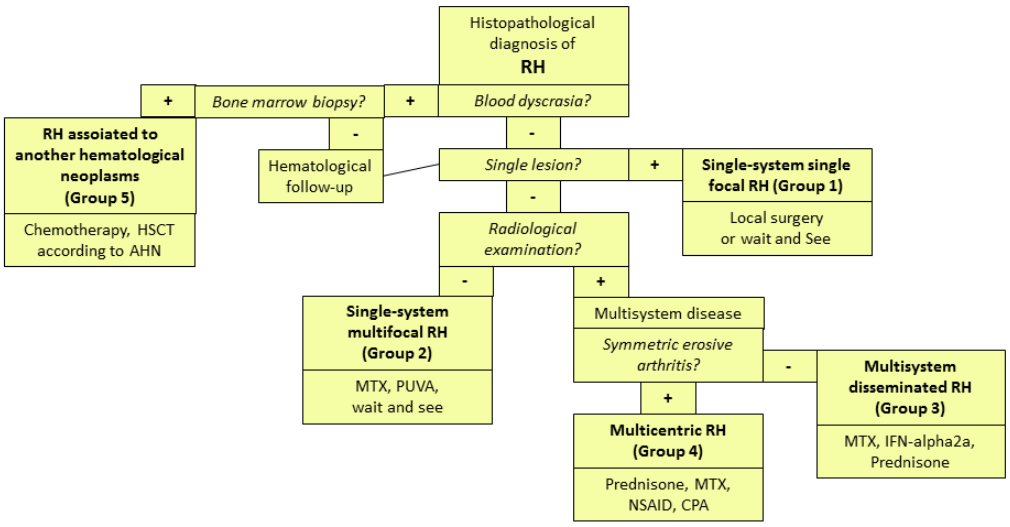

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