Uncommon Fibroinflammatory Sinonasal Tract Lesions

Granulomatosis with Polyangiitis, Eosinophilic Angiocentric Fibrosis, and Rosai–Dorfman Disease

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KEYWORDS

• Sinonasal tract pathology • Fibroinflammatory lesions • Granulomatosis with polyangiitis
• Eosinophilic granulomatosis with polyangiitis • Eosinophilic angiocentric fibrosis
• IgG_4-related disease • Rosai–Dorfman disease • Differential diagnosis

Key points

- Necro-inflammatory and fibroinflammatory lesions encompass a broad spectrum of diseases in the sinonasal tract.
- Granulomatosis with polyangiitis shows a very characteristic blue, granular, stromal biocollagenolytic necrosis.
- Eosinophilic angiocentric fibrosis has a unique onion-skin-like concentric perivascular hyalinization with heavy eosinophilic infiltrate.
- Rosai–Dorfman disease is a histiocytic disorder with large histiocytes, often showing lymphocytes in their cytoplasm, the lymphocytes creating a halo or clearing around them.

ABSTRACT

Fibroinflammatory lesions of the sinonasal tract include inflammatory polyps (chronic rhinosinusitis), various infectious, sarcoidosis, and NK/T-cell lymphoma as examples of the most commonly encountered lesions. However, the differential diagnosis includes several less frequently encountered entities, such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg–Strauss), eosinophilic angiocentric fibrosis considered part of IgG_4-related disease, and Rosai–Dorfman disease. This review focuses on these latter entities providing an update on clinical, laboratory, imaging, histology, and ancillary testing employed to reach an actionable diagnosis.

INTRODUCTION

Inflammatory lesions of the sinonasal tract (SNT) are one of the most common head and neck lesions submitted to surgical pathology. The majority represent the findings of chronic rhinosinusitis and inflammatory polyps.[1–5] However, within the

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fibroinflammatory and necro-inflammatory patterns, several distinct entities must be considered, as management and outcome are quite different and unique. Granulomatous inflammation, including necrosis and/or the presence of foreign body-type giant cells, storiform fibrosis, a rich eosinophilic infiltrate, and emperipolesis are unique findings that require evaluation for specific etiologies. The more common etiologies, such as reactive polyps and chronic rhinosinusitis, may show a diverse histologic spectrum and so isolated areas of necrosis, small eosinophilic abscesses or even giant cells should not be misinterpreted to be significant. Still, a keen sense of the spectrum of changes that can be seen will allow for a more in-depth evaluation and reaching a diagnosis of one of the more uncommon inflammatory-type disorders in selected cases. Care must be taken not to overinterpret surface ulceration and erosion due to manipulation or microtrauma, but instead to recognize when necrosis and fibroinflammatory changes are within the connective tissue stroma and are the root cause of the disorder. Selected necro-inflammatory and fibroinflammatory lesions will be reviewed herein.

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) is a systemic, immune complex mediated, cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA)-associated, necrotizing vasculitis primarily affecting small-to-medium vessels in the upper respiratory tract (URT) and kidneys.[6–10] Patients are usually middle-aged at presentation without a clear sex predilection,[11] affecting about 0.4 to 2 cases per 100,000 population. Symptoms are nearly always nonspecific sinusitis, often accompanied by constitutional symptoms of malaise, fever, chills, and weight loss. Using the ELK-classification (E: ear, nose, and throat involvement; L: lung involvement; K: kidney involvement)[12] helps with systemic stratification, as disease may remain limited and localized or progress to systemic involvement, with regression following effective treatment. Importantly, a substantial proportion of patients remain with limited, localized disease.[13] When systemic, patients are usually quite sick. The American College of Rheumatology has developed classification criteria for GPA, with 10 features evaluated in a weighted fashion.[6] The highest point weightings in the system are for nasal crusting, bloody nasal discharge and congestion, and c-ANCA or proteinase 3 (PR3)-ANCA. Symptoms include sinusitis, obstruction, pain, anosmia, and headaches, with other symptoms reflecting site-specific involvement. The nasal cavity is affected more often than the paranasal sinuses, while the nasopharynx, lacrimal gland and duct, larynx, oral cavity, and ear and temporal bone can also be affected.[14,15] Clinical examination demonstrates crusted ulcerations, purulent discharge, and erythematous mucosa often with granulation-type tissue. Disease progression may lead to perforation and collapse of the nasal cartilages, potentially leading to saddle nose deformity. Imaging studies are usually nonspecific but may show mucosal thickening, osteitis, and paranasal bone and/or septal erosion.[6,7,11,16–20] By serology, autoantibodies to lysosomal components of neutrophils, specifically the c-ANCAs associated with antibodies against PR3, are considered confirmatory in the correct clinical and histologic setting.[9,20,21] PR3 is the major target antigen of c-ANCA, directed against the neutral serine proteinase within the azurophil granules of neutrophils and monocyte lysosomal granules, and is considered highly specific for GPA. c-ANCA is considered quite specific, but it can be seen in other vasculitides, considered to directly induce vasculitis by activating neutrophils. The sensitivity varies with disease extent. c-ANCA negative cases account for up to 30% of patients with GPA, and thus, negative serology does not exclude the disease, with histologic evaluation considered the gold standard even when biopsies are “blind” (non-targeted).[22,23] Importantly, the titer can be used to monitor disease progression or remission, although with a latency of up to 8 weeks and sometimes with fluctuations.[13,24,25]

The histologic triad of GPA is biocollagenolytic (necrobiotic) necrosis, granulomatous inflammation, and vasculitis, but in daily practice, all 3 are seen simultaneously in fewer than 20% of patients,[26,27] with usually only one or two features present, resulting in “consistent with” or “suggestive of” diagnoses. “Biocollagenolytic” necrosis refers to stromal connective tissue regions of geographic, ischemic-type basophilic necrosis composed of dead neutrophils creating granular to smudgy debris (**Fig. 1**A). Well-formed granulomatous inflammation is scant to absent in most biopsies, while isolated multinucleated giant cells (**Fig. 1**B) are uncommonly seen.[28] The polymorphous inflammatory infiltrate is composed of lymphocytes, histiocytes, and plasma cells, often with eosinophils and polymorphonuclear leukocytes, the latter two predominating in some cases. Vasculitis affects small-to-medium-sized vessels, starting off as fibrin deposition within and around vessels, a result of destroyed endothelium initiating the coagulation cascade with plasma proteins accumulating as fibrin, followed by inflammatory cells surrounding

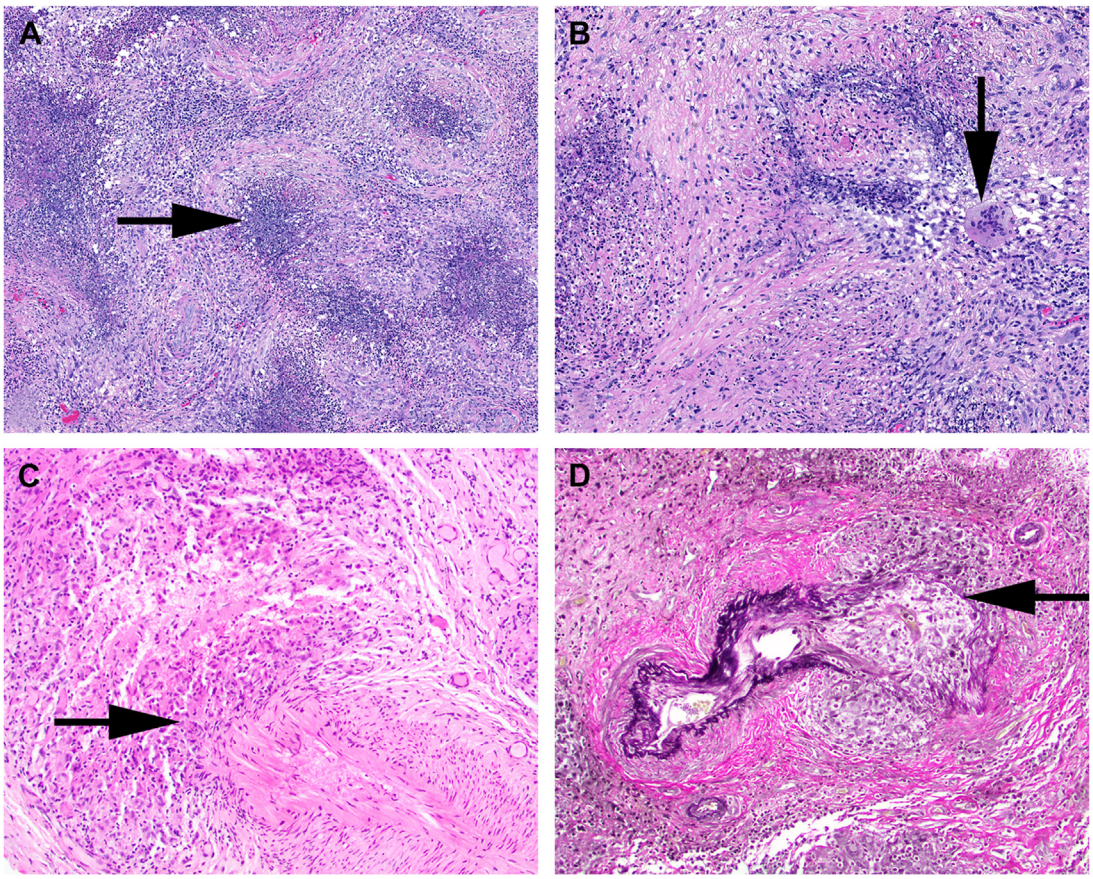

Fig. 1. Granulomatosis with polyangiitis (GPA). (*A*) Blue, granular, stromal biocollagenolytic necrosis (*black arrow*) is quite characteristic in the head and neck for GPA. (*B*) Isolated multinuclear giant cells (*black arrow*) may be seen. (*C*) Destruction of the vessel wall (*black arrow*) by inflammatory cells represents vasculitis. (*D*) The destroyed vessel wall can be highlighted with an elastic stain, showing the loss of the elastic lamina (*black arrow*).

(angiocentric) and infiltrating through the vessel wall (angiodestructive; **Fig. 1**C), including eosinophils. Well-developed vasculitis is difficult to detect in most biopsies; sometimes it can be highlighted by elastic stains (**Fig. 1**D).

The most important differential is with various infectious agents (bacteria including acid-fast organisms, fungi, viruses, protozoa), which must be actively excluded by histochemistry testing, laboratory investigation, and even using molecular techniques.[29] Infections are suggested as a cofactor in disease development and bacterial superinfection may be seen, but commensal organisms and surface contamination must be eschewed, limiting interpretation to deep stromal connective tissue sites. IgG_4-positive plasma cells may be increased in GPA, but IgG_4-related disease (IgG_4-RD) does not have biocollagenolytic necrosis and usually has storiform fibrosis, while presenting with different clinical symptoms and serologies.[30] SNT involvement is uncommon in patients with Crohn disease and is not usually the initial presentation. Sarcoidosis is a systemic disorder characterized by very tight, well-formed epithelioid granulomas with giant cells, asteroid bodies, and sometimes calcifications, generally lacking coagulative necrosis.[31–33] Langerhans cell histiocytosis is a histiocytic neoplasm characterized by enlarged, reniform nuclei showing nuclear membrane lobations or indentations and septations, lacking necrosis, and associated with a predominantly eosinophil-rich inflammatory infiltrate. The lesional cells are immunoreactive with CD1a and langerin (CD207).[34,35] Erdheim–Chester disease is a systemic histiocytic neoplasm of mature histiocytes within a fibrosclerotic background. Xanthelasma-like lesions of the periorbital tissues and sinonasal sclerosis on imaging are common findings. Still, the bland foamy histiocytes with background chronic inflammatory cells,

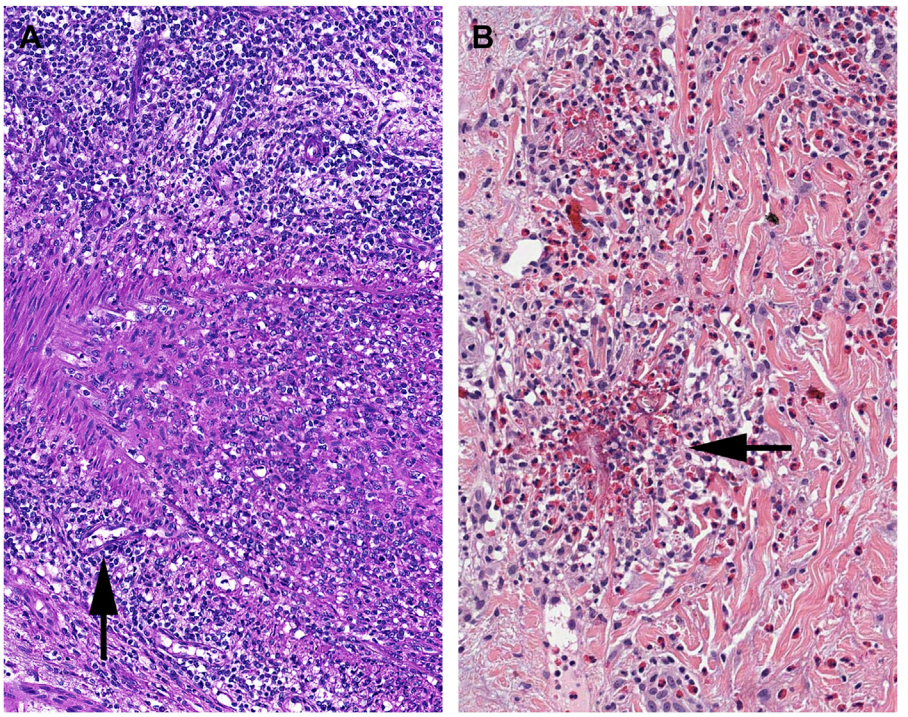

Fig. 2. The differential for GPA includes (*A*) an NK/T-cell lymphoma, which shows atypical lymphocytes destroying the vessel wall (angiodestructive and angiocentric; *black arrow*). (*B*) Eosinophilic granulomatous vasculitis (Churg–Strauss) tends to show a much more prominent eosinophilic infiltrate (*black arrow*) but requires clinical, radiologic, and pathologic correlation.

Touton-type giant cells, and marked fibrosis without necrosis or any significant eosinophilic infiltrate help with the separation.[36] Sinonasal cocaine abuse may show nonspecific ulcers but lacks vasculitis or fibrosis, while occasionally, polarizable foreign-body material (used to cut cocaine) may be identified.[37–40] Lymphoid or histiocytic cells with pleomorphism, angiocentric destruction, and tumor necrosis suggest a hematolymphoid malignancy (**Fig. 2**A), which can be further worked up by immunohistochemistry, flow cytometry, and/or molecular techniques to identify NK/T-cell lymphoma, EBV-associated lymphomas, and diffuse large B-cell lymphomas of various subtypes.

Finally, the separation from eosinophilic granulomatosis with polyangiitis (EGPA; Churg–Strauss) may be very difficult in routine practice. Defined as a systemic disease that mainly affects the respiratory tract, it is characterized by asthma, blood eosinophilia, and vasculitis (**Fig. 2**B). Still, when applying the American College of Rheumatology classification criteria for GPA, many patients with EGPA show a total score of 5 points or greater[6] and would be potentially misclassified. Most patients present with head and neck manifestations[41] but show a higher concentration of eosinophils ($\geq$1 x 10^9/L) and tend to show an anti-myeloperoxidase ANCA.[32,41–44] Still, surgery, systemic steroids, and immunomodulation agents are used to treat, and thus, overlapping features and response to therapy may blur some of these distinctions.[42,45]

Treatments of GPA include various cycling of antibiotics, methotrexate, cyclophosphamide, rituximab, and steroid therapies, with noncosmetic functional procedures indicated in only a few patients who have failed maximal medical options.[46,47] Combination treatments achieve good remission rates, but relapses may be seen years after remission, and thus, patients remain under surveillance throughout their lives. Generally, patients with ear, nose and throat (ENT) localized disease have a better overall prognosis and may not develop renal disease, the latter a major source of morbidity and mortality.[9]

EOSINOPHILIC ANGIOCENTRIC FIBROSIS (IgG_4-RELATED DISEASE)

Eosinophilic angiocentric fibrosis (EAF) is a very rare, chronic, tumefactive, obstructive orbit and/or upper aerodigestive tract lesion considered a

candidate for IgG4-RD, with a submucosal inflammatory and fibrosing reaction.[32,39,48–55] It is a unique SNT lesion, with similar histologic features seen in granuloma faciale, with some considering it to be the mucosal subtype of granuloma faciale, where adaptive immunity and cytotoxic granules seem to have a role in pathogenesis.[56] In fact, concurrent granuloma faciale is seen in about a quarter of patients.[48,56–59] Female individuals are affected more often than male individuals, presenting in the fifth decade of life most frequently with progressive and prolonged airway obstruction, often after decades of symptoms.[51,60] Additional symptoms include allergies, urticaria, and drug sensitivities, with up to a third of patients having a history of trauma or previous nasal surgery.[53,54,61] Pain, epistaxis, dyspnea, epiphora, visual changes, and/or proptosis are infrequently noted.[54,60] With time, anterior nasal cavity, and especially septal involvement, results in nasal deformity (saddle nose), with frequent extension into the paranasal sinuses and orbit. Unilateral disease may expand to be bilateral over time.[54,60,62] The disease may follow a waxing and waning clinical course with periods of stabilization, but it is not ever cured. Most patients have an elevated serum IgG4 concentration (>135 mg/dL), but importantly, systemic findings or multiorgan system disease is absent.[51,55,63] Curiously, circulating plasmablast counts are elevated in active disease and decrease with treatment,[39] although not considered specific for IgG4-RD. PR3-ANCA and myeloperoxidase-ANCA levels are not elevated. Nasal endoscopy shows tan-white, fleshy to gritty-fibrotic submucosal masses, occasionally with ulceration. By imaging, lesions are sizeable (mean about 30 mm), appearing isointense to gray matter, showing moderate inhomogeneous post-contrast enhancement.[64]

Histologically, EAF is best recognized by concentric layered onion-skin-type, dense, sclero-hyaline fibrosis around submucosal capillaries, venules, and small arteries (angiocentric), with a mixed inflammatory infiltrate but eclipsed by eosinophils (**Fig. 3**A). Some areas may show a more storiform or whorled fibrosis rather than concentrically laminated. An obliterative phlebitis is the result of fibrosis, a feature of IgG4-RD. There is a temporal development over time with more fibrosis around the chronically injured vessels (**Fig. 3**B) until the inflammatory infiltrate volume is reduced, although eosinophils generally remain. Still, multiple phases may be seen in the same biopsy. Early phase tends to show more eosinophils within and around capillaries and venules, with a lymphoplasmacytic infiltrate concurrently present to a variable degree. With time, the concentric layering of hypocellular fibrosis becomes prominent (**Fig. 3**C). Several important negatives are noted: no ischemic necrosis, no biocollagenolytic necrosis, no nuclear dust, no granulomatous inflammation, and no multinucleated giant cells.[49,52,59] Generally, greater than 50 IgG4-positive plasma cells in a high power field (40x magnification; **Fig. 3**D) help to confirm the diagnosis, along with an IgG4(+) plasma cells to IgG(+) plasma cells ratio (IgG4:IgG) of greater than 40%. An elastic stain highlights vessel wall destruction, although sometimes difficult to interpret. By definition, special stains for microorganisms should be negative (**Fig. 4**A).

While this concentric, laminated fibrosis and rich eosinophilic infiltrate is quite unique in the head and neck, infections, EGPA (Churg–Strauss disease), desmoid-type fibromatosis, Kimura disease, solitary fibrous tumor, inflammatory myofibroblastic tumor (**Fig. 4**B), epithelioid hemangioma (**Fig. 4**C), follicular dendritic sarcoma (**Fig. 4**D), and even ECD may be considered. By definition, infectious etiologies are evaluated and excluded by a variety of testing methods and are beyond the scope of this review, but fibrosis is generally not a prominent feature; the classical large vacuolated histiocytes of rhinoscleroma (see **Fig. 4**A) are not seen in EAF.[43,65] In these differential diagnoses, pertinent immunohistochemistry studies (nuclear ß-catenin in fibromatosis[66]; STAT6 in solitary fibrous tumor[67]; ALK and SMA in inflammatory myofibroblastic tumor[68]; FOSB by immunohistochemistry in epithelioid hemangioma[69]; CD21, CD23, and CD35 in follicular dendritic cell sarcoma[70]; CD163 and CD68 in ECD[71]) would aid in these distinctions. Kimura disease affects lymph nodes, shows prominent germinal centers, eosinophilic microabscesses, and lacks any whorled fibrosis.[72] Granulomatous inflammation with giant cells and eosinophils is more prominent in Churg–Strauss disease, an uncommon URT disorder associated with asthma.[42] Hodgkin lymphoma may have eosinophils and sclerosing fibrosis, but the classical Reed–Sternberg cells and other inflammatory milieu would aid in distinction. Cocaine abuse is generally a clinical differential, as the histologic findings are nonspecific inflammation, a giant cell reaction, and often polarization foreign-body material that is used to cut the drug.[37] Skin-based granuloma faciale can have similar features, although nuclear dust is often present around the vessels and concentric fibrosis is limited to absent.

The treatment usually resolves around surgery, as response to steroid therapy is inconsistent and thus raises the question of whether this lesion is truly part of IgG4-RD.[51,53,54,60,61] Still, the

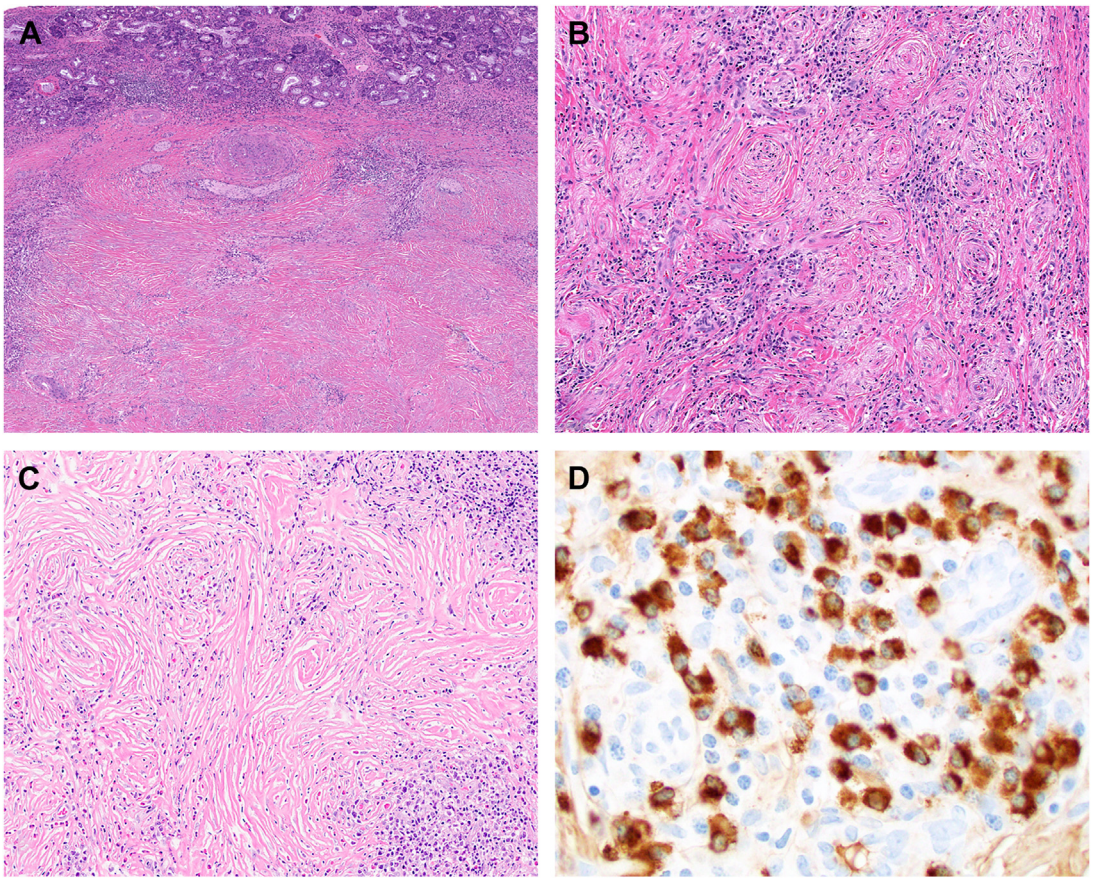

Fig. 3. Eosinophilic angiocentric fibrosis (EAF). (*A*) The deep stroma demonstrates a very heavy stromal sclerotic fibrosis associated with a mixed inflammatory infiltrate. (*B*) There is a perivascular collagen deposition associated with mixed inflammation, including eosinophils. (*C*) The characteristic onion-skin-type perivascular hyalinization is noted along with eosinophils. (*D*) There are greater than 50 IgG_4-positive plasma cells that are one of the features suggesting IgG_4-RD.

disease follows a progressive and relentless clinical course with multiple recurrences, often showing a potentiating of the disorder after surgery.[49,51,52,54,56,59,61,73–75] Disease stabilization is eventually noted with surgery often the best management.

ROSAI–DORFMAN DISEASE

Rosai–Dorfman disease (RDD; Destombes–Rosai–Dorfman syndrome; sinus histiocytosis with massive lymphadenopathy) is an uncommon histiocytic disease characterized by the accumulation of abnormal, S-100 protein-positive histiocytes showing emperipolesis.[76–79] This abnormal histiocytic proliferation is not well understood, although a significant subset is probably neoplastic showing pathogenic variants in the mitogen-activated protein kinase/extracellular signal-related kinase pathway, with *KRAS*, *ARAF*, *CSF1R*, and *MAP2K1* identified.[80,81] Of additional note, is the uncommon association with constitutional pathogenic variants (germline mutations) in *SLC29A3*, a familial inherited form of RDD sometimes part of H syndrome or an autoimmune lymphoproliferative syndrome (*TNFRSF6* associated).[82–85]

Whereas the cervical lymph nodes are a common site of involvement, it is the extranodal manifestations in the SNT and orbit that are to be considered here,[77,86–91] identified in up to 40% of patients. There is an equal sex distribution with patients from all ages affected, although with a mean age at presentation in the third decade,[77,89] although male patients are more commonly affected in pediatric patients.[91] Symptoms are generally nonspecific, and while lymphadenopathy is identified with nodal disease, extranodal SNT manifestations are referrable to obstruction, mass lesion, proptosis, ptosis, pain, and even cranial nerve deficits. Systemic symptoms (fever, chills, night sweats,

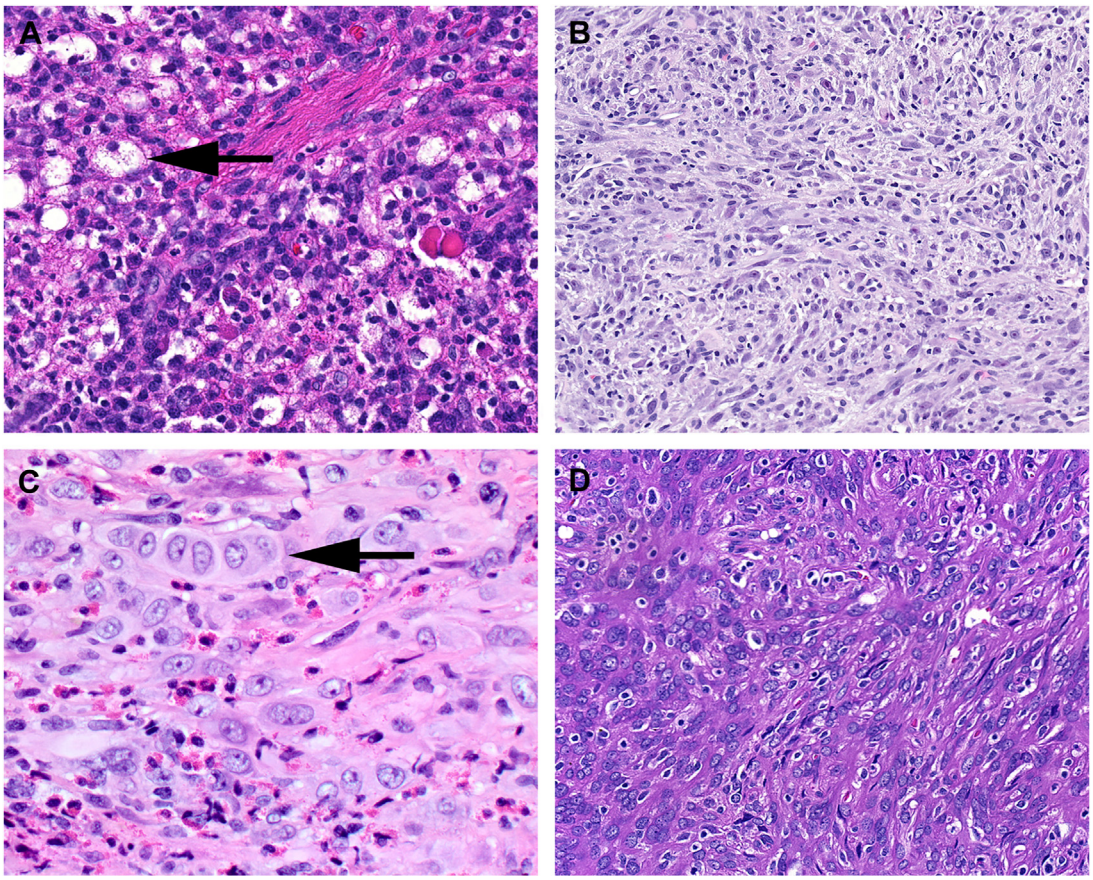

Fig. 4. The differential diagnosis for EAF includes (*A*) rhinoscleroma where the infectious organisms are identified within the Mikulicz cells (*black arrow*). (*B*) Inflammatory myofibroblastic tumor shows a spindled cell population with tadpole to ganglion-like cells and a mixed inflammatory infiltrate. (*C*) Epithelioid hemangioma shows epithelioid vessels (*black arrow*), with a rich eosinophilic infiltrate. (*D*) Follicular dendric cell sarcoma shows atypical spindled cells with vesicular nuclei associated with an inflammatory cell infiltrate.

weight loss) are seen in some patients.[77,81,87–92] Endoscopy shows mucosal thickening and sometimes a polypoid or nodular growth. Imaging findings are usually nonspecific, with homogeneously enhancing soft-tissue density masses.[92,93] Hematology evaluation may show anemia, polyclonal hypergammaglobulinemia, leukocytosis, and thrombocytopenia, along with a generally elevated erythrocyte sedimentation rate, but none are specific to the disease.[81] Aspiration of SNT disease is uncommon, but lymph node cytology shows lymphocytes, plasma cells, and large histiocytes, the latter frequently with emperipolesis.[94,95]

The histologic features are composed of sheets of submucosal lymphoid aggregates with clusters or nests of pale, large, histiocytic cells (**Fig. 5**A). The lymphocytes and plasma cells are nondescript without pleomorphism or monotony, although Mott cells and Russell bodies (intracytoplasmic eosinophilic globules) may be identified. Germinal centers are usually scant to absent. The histiocytic cells are large, with abundant foamy to clear-appearing cytoplasm surrounding nuclei that may be indented, lobulated, or showing a longitudinal groove (**Fig. 5**B). Phagocytized cells (usually lymphocytes or plasma cells but can be erythrocytes or neutrophils) within the histiocytes' cytoplasm are characteristic although seen less frequently than in nodal disease.[77,83,91,94,96] Isolated histiocytes with emperipolesis are difficult to see, but emperipolesis of many cells is not uncommon, expanding the cell size. Generally, granulomas, multinucleated giant cells, eosinophils, dense fibrosis, and vasculitis are absent in extranodal disease. The lesional histiocytes may be reactive with CD68 (KP1), lysozyme, OCT2, and CD163, while strongly reactive with S100 protein,[80,83,97] the latter often showing a halo around the engulfed cells (**Fig. 5**C). There is no reactivity with CD1a or CD207, and there is a polyclonal kappa and lambda expression.

It is most important to exclude an infectious etiology, including rhinoscleroma, while IgG_4-RD and

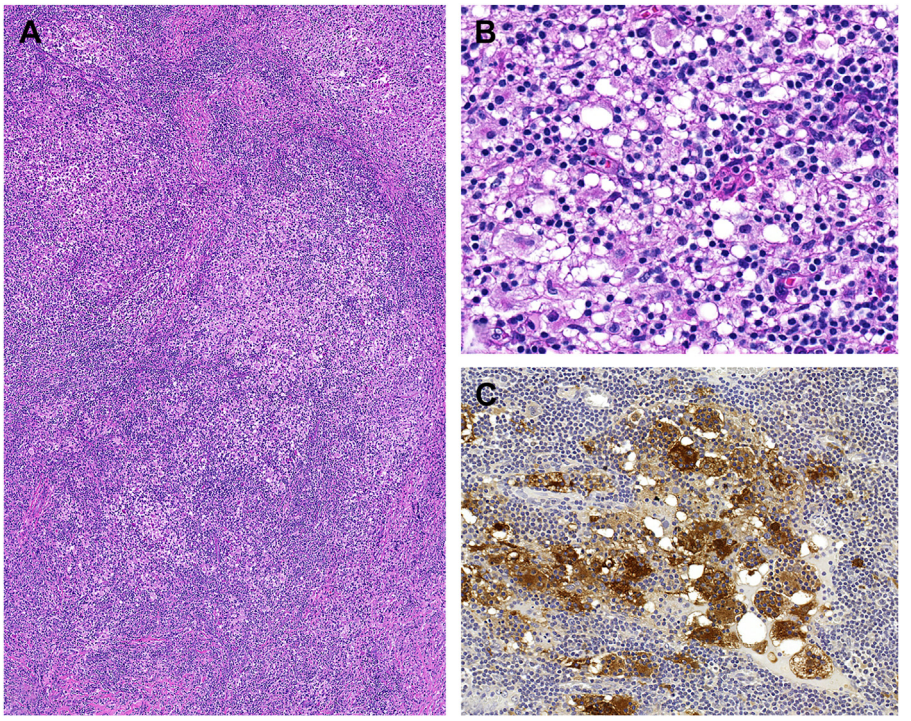

Fig. 5. RDD shows (*A*) sheets of large histiocytes in a rich inflammatory cell background. (*B*) Emperipolesis is demonstrated by lymphocytes within the histiocyte's cytoplasm (often with a halo). (*C*) S100 protein highlights the abnormal, large histiocytes.

other histiocytic disease must be considered. Rhinoscleroma may show emperipolesis, but the presence of organisms filling the "Mikulicz" cells is characteristic (see **Fig. 4**A).[65,75,98] Interestingly, up to 20% of patients will have an elevated IgG_4/IgG-positive plasma cell ratio of greater than 40%,[79] a finding that must be taken into consideration when evaluating the differential diagnosis with IgG_4-RD. Langerhans cell histiocytosis is a neoplastic proliferation of dendritic-type Langerhans cells, but the characteristic coffee-bean-shaped nucleus, strong association with eosinophilic infiltrate, and the well-known *BRAF* pathogenic variants, along with strong CD1a and CD207 (langerin, part of the Birbeck granule in the cytoplasm) immunoreactivity can help with separation from RDD.[34,35,99]

Many patients experience spontaneous regression, and thus, observation after diagnosis can be employed, although surgery is usually performed to achieve the diagnosis. Relapse can be seen, but generally, it is only if the disease extends to involve vital structures that morbidity develops. If there is disseminated nodal disease or development of another hematolymphoid disorder, the prognosis may be more guarded.[77,78,81,87,88,91] Targeted therapies show promise.[78] In some instances, exclusion of familial disease is recommended.[82]

SUMMARY

Understanding and including in the differential diagnoses of necro-inflammatory lesions that affect the SNT, disorders like GPA, EAF, and RDD, will use a systematic approach to diagnosis. Implementation of selected histochemistry and immunohistochemistry studies will allow for a definitive diagnosis to be achieved and appropriate management initiated.

CLINICS CARE POINTS

- GPA is a vasculitis that is frequently limited to the upper aerodigestive tract and demonstrates biocollagenolytic necrosis, isolated multinucleated giant cells with associated necrotizing vasculitis in patients who generally show PR3-ANCA association.
- EAF is made up of tumefactive sclero-hyaline concentric perivascular fibrosis with a rich eosinophilic infiltrate in patients who frequently show IgG_4-RD plasma cell findings but without development of systemic disease.
- RDD may be a limited abnormal histiocytic disease showing abnormal S100 protein-positive histiocytes generally demonstrating emperipolesis.

PATHOLOGIC KEY FEATURES

Key pathologic features of uncommon SNT necro-inflammatory lesions

- GPA shows biocollagenolytic necrosis and vasculitis.
- EAF shows concentric laminated sclerotic fibrosis around small vessels with rich eosinophilic infiltrate.
- RDD has large, vacuolated histiocytes with emperipolesis in a rich inflammatory cell background.

DISCLOSURE

The author declares that he has no conflict of interest as it relates to this review. This review article was performed in accordance with ethical standards and did not require informed consent. Consent to participate or for publication was waived as it is a review article without any uniquely identifying personal data. The opinions or assertions contained herein are the private views of the author.

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