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Algorithmic Approach to Fibroinflammatory Sinonasal Tract Lesions

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Abstract
Fibroinflammatory lesions of the sinonasal tract are one of the most common head and neck lesions submitted to surgical pathology. When the fibroinflammatory pattern represents the lesion (i.e., not surface reactive ulceration), an algorithmic approach can be useful. Separated into reactive, infectious, and neoplastic, and then further divided based on common to rare, this logical progression through a series of differential considerations allows for many of these lesions to be correctly diagnosed. The reactive lesions include chronic rhinosinusitis and polyps, granulomatosis with polyangiitis, and eosinophilic angiocentric fibrosis. Infectious etiologies include acute invasive fungal rhinosinusitis, rhinoscleroma, and mycobacterial infections. The neoplastic category includes lobular capillary hemangioma, inflammatory myofibroblastic tumor, and NK/T-cell lymphoma, nasal type. Utilizing patterns of growth, dominant cell types, and additional histologic features, selected ancillary studies help to confirm the diagnosis, guiding further clinical management.

Keywords Sinonasal tract · Fibroinflammatory lesions · Eosinophilic angiocentric fibrosis · Granulomatosis with polyangiitis · Chronic rhinosinusitis · Mycobacterial pseudotumor · Rhinoscleroma · Differential diagnosis

Introduction

Fibroinflammatory lesions of the sinonasal tract 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. However, within the fibroinflammatory pattern, several distinct entities must be considered as management and outcome are quite different and unique. When the wrong diagnosis is made, surgical management versus supportive versus antimicrobial treatment results in an untoward outcome. An approach to such lesions is first to recognize that there is a mixed inflammatory infiltrate associated with a background of spindled cells. While surface ulceration over squamous cell carcinoma and other spindled cell neoplasms must be excluded, it is when the fibroinflammatory pattern represents the lesion that an algorithmic approach can be useful. Separated into reactive, infectious, and neoplastic, and then further divided based on common to rare, this logical progression through a series of differential considerations (Fig. 1) allows for many of these lesions to be correctly diagnosed.

Case Presentation

A 35-year-old woman presented with worsening nasal obstruction. There was some tenderness and swelling involving the nares. There was no history of asthma, although she had reported allergies. By endoscopy, there was a firm, symmetric swelling without normal cartilage mobility. The nasal airway was obstructed. By imaging, there was occlusion of the anterior-most airway at the level of the vestibule and inferior turbinate, right sided more than the left. Laboratory studies had not been performed. This was her third biopsy in 2 years, with the first two samples called "chronic rhinosinusitis." Histologically, there was only lesional tissue (Fig. 2a). The inflammatory infiltrate was comprised of a full spectrum of cells, including lymphocytes, plasma cells, histiocytes, and acute inflammatory cells, with easily identified eosinophils (Fig. 2b). The inflammatory component was identified around the walls of a number of vessels, but a true vasculitis was not identified: there was no fibrinoid

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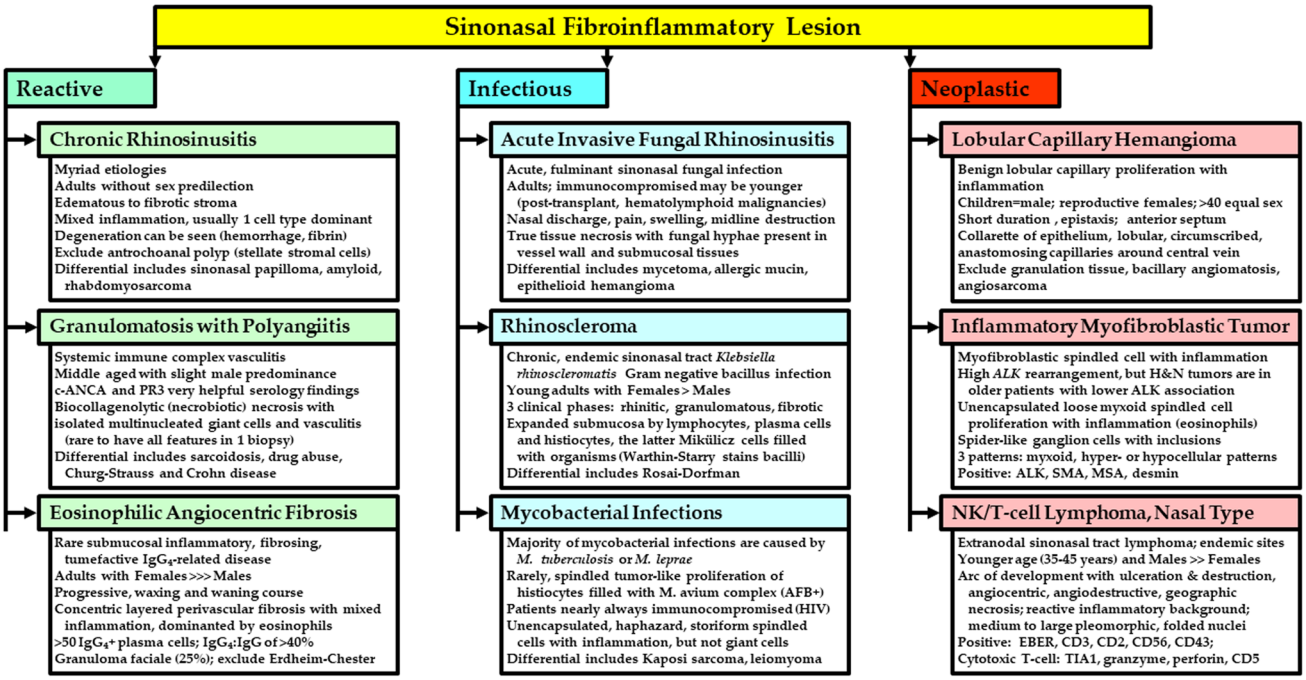

Fig. 1 A representation of several major categories to consider in the evaluation of sinonasal tract fibroinflammatory lesions

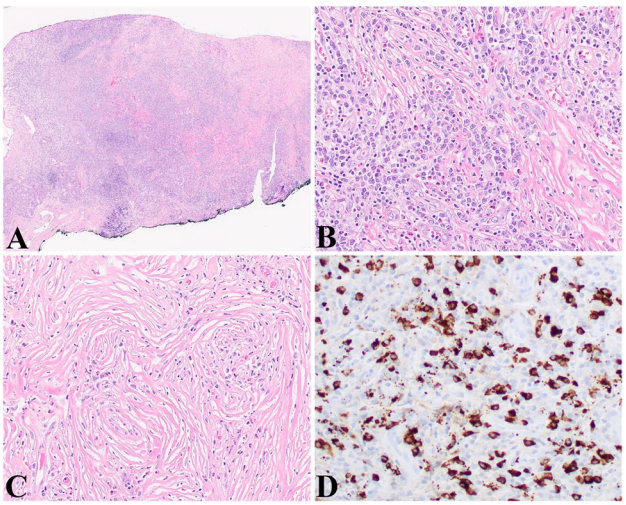

Fig. 2 Eosinophilic angiocentric fibrosis. **a** A polypoid fragment of tissue with a fibroinflammatory proliferation. **b** There is stromal collagen deposition with a mixed inflammatory infiltrate, including eosinophils. **c** Onion-skin-type perivascular hyalinization is characteristic. **d** There are > 50 IgG_4-positive plasma cells in a high power field

necrosis, no leukocytoclastic reaction, no areas of nuclear dust, and no extravasated erythrocytes. There was no vascular proliferation or phlebitis. The endothelial cells were not raised or enlarged. Giant cells were not appreciated. There was a well-developed fibrosis, heavily deposited in some areas, while sparse in others. In the heaviest areas, there was a concentric "onion-skin" whorling of the collagen around the vessels (Fig. 2c). Biocollagenolytic necrosis was not seen. Special studies for fungal and AFB organisms were negative. The plasma cell population was polytypic for kappa and lambda, with a mixture of B- and T-cells. No polarizable foreign body material was present. Not wanting to render a "nonspecific" diagnosis, the case was submitted for consultation hoping to obtain a more definitive diagnosis. IgG and IgG_4 immunohistochemistry demonstrated > 50 IgG_4-positive plasma cells (Fig. 2d), with a ratio of about 60% of IgG_4:IgG. The lesion was completely excised, and she has received intralesional steroid therapy. Serum IgG_4 levels were not elevated. Clinical consideration was given to Rituximab therapy, but with clinical improvement after surgery and steroids, no additional therapy has been undertaken to this point.

Differential Diagnosis

Reactive

The reactive category includes chronic rhinosinusitis, inflammatory sinonasal tract polyps, granulomatosis with polyangiitis, and eosinophilic angiocentric fibrosis, recognizing that other reactive conditions may also be seen. Importantly, surface ulceration with reactive fibrosis and mixed inflammation is a common finding due to friction or digital manipulation (such as nose picking, pencils,

cotton-tipped applicators, nasal hair scissors or tweezers, decorative piercing, foreign body, or the like). Traumatic lesions are more frequently unilateral than bilateral. Erosion or ulceration overlying a neoplasm must also be excluded. However, once it is recognized that the lesion is fibroinflammatory, then further investigation can be undertaken.

Chronic Rhinosinusitis and Polyps

Chronic rhinosinusitis is an inflammation of the nasal cavity and/or paranasal sinuses. There are a myriad of etiologies (allergies, infection, aspirin, toxins, medications) as well as idiopathic [1–3]. Patients tend to be adults without sex predilection. Symptoms are usually nasal obstruction and discharge, often bilateral. Viral and bacterial forms of acute rhinosinusitis are not usually biopsied, and it is only when chronic (> 12 weeks) that biopsy may be employed. The sinonasal mucosa is edematous and pale, and if concurrent polyps are present, may yield a polypoid appearance. Antrochoanal polyps are usually seen in younger males, and are typically unilateral.

Histologically, the surface may show metaplastic squamous epithelium, while the submucosa is edematous with a mixed inflammatory infiltrate (Fig. 3a). The inflammatory cells include lymphocytes, plasma cells, macrophages, and eosinophils, the latter predominant in allergic disease (Fig. 3b). Acute inflammation is more likely seen in a bacterial etiology. Fibrosis is limited, although may be more prominent with chronicity. Over time, inflammatory sinonasal polyps may develop, which often show a thickened basement membrane, and either a lymphoplasmacytic or eosinophilic predominant infiltrate (Fig. 3b). A prominent submucosal hemorrhage with fibrin deposition or infarction may be seen in degenerative polyps [4]. Spindled cells are generally absent, but isolated stellate fibroblasts with hyperchromatic nuclei may be seen below the surface epithelium or perivascular, considered a degenerative phenomenon. They do not form sheets or show increased mitoses, a finding more likely in embryonal rhabdomyosarcoma (also myogenin or myo-D1 reactivity, not just desmin or smooth muscle actin). Prominent fibrosis or fibrin may mimic amyloid, but the acellular, extracellular, smudged eosinophilic quality of amyloid can be confirmed with a Congo red stain in selected cases. Sinonasal papilloma may have inflammation, but show a proliferative transitional-type epithelium, endo- or exophytic growth, and intraepithelial microabscesses.

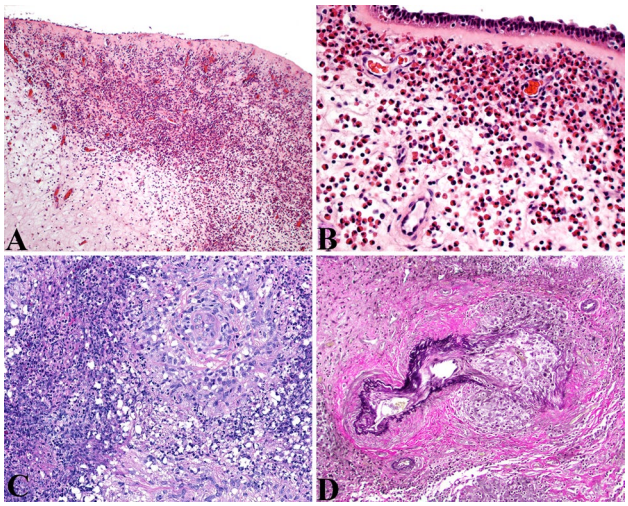

Fig. 3 **a** An inflammatory sinonasal polyp with edematous stroma and inflammatory infiltrate. **b** There is a thickened basement membrane and numerous eosinophils in this inflammatory polyp. **c** Granulomatosis with polyangiitis (GPA) showing perivascular inflammation with blue, granular biocollagenolytic debris. **d** An elastic stain highlights destruction of a vessel wall, with inflammatory cells in the background of this GPA case

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) is a systemic immune complex vasculitis affecting the sinonasal tract and kidneys most commonly [5]. Patients affected are usually middle aged with a slight male predominance. Symptoms are non-specific sinusitis and often constitutional findings, with clinical examination demonstrating ulceration with crusting, sometimes progressing to perforation and collapse of the nasal cartilages. By serology, autoantibodies to lysosomal components of neutrophils, specifically the cytoplasmic antigen (antineutrophil cytoplasmic antibodies; c-ANCA) associated with antibodies against proteinase 3 (PR3) is considered confirmatory in the correct clinical and histologic setting [6].

The histologic triad of GPA is biocollagenolytic (necrobiotic) necrosis, granulomatous inflammation, and vasculitis, but all three features are seldom seen concurrently [7, 8]. “Biocollagenolytic” or “necrobiotic” necrosis refers to zones of geographic basophilic necrosis with granular, cellular debris usually of neutrophils (Fig. 3c). Isolated giant cells may be seen, but well-formed granulomatous inflammation is usually sparse to absent. Vasculitis affects small to medium sized vessels and is the most specific finding, but is difficult to detect in most cases (Fig. 3d). Fibrin in the wall rather than full thickness involvement is more frequent. Most biopsies show non-specific acute and chronic inflammation with eosinophils and sometimes neutrophilic microabscesses. Elastic stains may highlight affected vessels (Fig. 3d), while infectious disease studies are negative. Churg-Strauss disease shows granulomatosis and vasculitis as an allergic reaction, and generally shows tissue and peripheral eosinophilia, with pulmonary disease commonly concurrently present. Crohn disease may occasionally manifest with sinonasal tract granulomatous findings, but this

can be evaluated clinically. Cocaine abuse may show nonspecific ulcers, but does not have vasculitis or fibrosis, while occasionally polarizable material from talc or other material used to "cut" cocaine can be identified [9]. Sarcoidosis shows tight, well-formed granulomas, seldom with coagulative necrosis.

Eosinophilic Angiocentric Fibrosis (IgG_4-Related Disease)

Eosinophilic angiocentric fibrosis (EAF) is a rare, chronic obstructive upper aerodigestive tract lesion thought to be part of IgG_4-related diseases that demonstrates a submucosal inflammatory, fibrosing, and tumefactive reaction [10–13]. Patients are usually adults (5th decade), with females affected more often than males, presenting with progressive and prolonged airway obstruction (up to 20 years). The disease seems to progress and stabilize, but not ever resolve. The patients present with septal disease most often, but over time, involvement of the lateral wall and paranasal sinuses, orbit, and subglottic area may be seen. There is often an elevated serum IgG_4 concentration (> 135 mg/dL), but systemic disease is usually absent. PR3-ANCA levels are not elevated. About 25% of patients have concurrent granuloma faciale [14]. Endoscopically, the lesions are tan-white to pink, fleshy to fibrotic submucosal masses, occasionally with ulceration.

Histologically, EAF is characterized by concentric layered onion skin-type fibrosis around capillaries, venules, and small arteries, with a mixed inflammatory infiltrate dominated by eosinophils (Fig. 2a and c). The disease usually shows an arc of development over time, with a temporal evolution between vasculitis and fibrosis, with deposition of more and more fibrosis around the chronically injured vessels and a commensurate decrease in inflammation. However, both phases can be seen in the same biopsy. The laminated, scalloped fibrosis creates an onion-bulb appearance (Fig. 2c), quite unique in the sinonasal tract. The fibrosis is occasionally storiform to whorled with spindled fibroblasts giving a pseudogranulomatous appearance. The perivascular fibrosis results in an obliterative phlebitis, one of the features of IgG_4-related diseases. Early in the disease there are eosinophils within the capillaries and venules (Fig. 2b). A lymphoplasmacytic infiltrate may be seen. There is no necrosis, biocollagenolytic necrosis, granulomatous inflammation, or multinucleated giant cells [10, 13, 15]. Special stains for microorganisms are negative, but an elastic stain may highlight vessel wall destruction. Generally, > 50 IgG_4-positive plasma cells in a high power field (40x magnification) helps to confirm the diagnosis (Fig. 2D), along with an IgG_4(+) plasma cells to IgG(+) plasma cells ratio (IgG_4:IgG) of > 40%. If the fibrosis is misconstrued to be a spindled cell neoplasm, fibromatosis, solitary fibrous tumor, and schwannoma may be considered. Epithelioid hemangioma may have eosinophils, but shows high endothelial cells and lymphoid cells without significant fibrosis. Granuloma faciale is almost always on the face, but mucosal disease is exceedingly uncommon. While eosinophils are prominent, nuclear dust is easily recognized, while concentric fibrosis is usually absent. Erdheim-Chester, a multiorgan, neoplastic histiocytic disorder of CD68 positive, non-Langerhans histiocytosis (CD1a and S100 protein negative) shows fibrosis with histiocytes, but seldom affects the upper aerodigestive tract and usually lacks eosinophils, while many show *BRAF* V600E.

Infectious

Many infections can affect the sinonasal tract, with viral and bacterial causes the most common. These, however, seldom give cause for clinical concern or biopsy. However, selected infectious agents in the sinonasal tract do have unique features which are highlighted here.

Invasive Fungal Rhinosinusitis

Acute invasive fungal rhinosinusitis (AIFRS) is an acute and fulminant, often life-threatening sinonasal tract infection that results in destruction of the sinonasal tract over a very short time (days), often with skull base extension [16–18]. The majority of cases are caused by *Aspergillus* species (> 800 species are recognized) [19] but many other fungi are implicated. Patients are usually adults, although younger immunocompromised patients may also be affected, especially patients who are diabetic, being treated for hematolymphoid malignancies, and post-transplantation. Patients present with nasal discharge, facial/sinus pain, facial swelling, and with disease progression, even blindness. Serum fungal antigen testing may aid in diagnosis.

Histologically, there is true tissue necrosis and vessel wall involvement (Fig. 4A), but often without a significant inflammatory response due to the rapid clinical onset. Fungal hyphae are seen within mucosal and submucosal tissues as well as in and around vascular spaces (angioinvasive; Fig. 4a). Aspergillus hyphae are thin (2–5 μm) with acute angle branching (45°) and septations that can aid in identification [16, 17, 20]. Special studies, including periodic acid-Schiff stain (Fig. 4b) with fungal control or Gomori methenamine silver (GMS), in situ hybridization (using specific fungal probes), and PCR can effectively identify fungi in invasive fungal sinusitis as well as in species identification in specimens with negative cultures [21]. A mycetoma is just a fungal ball without tissue invasion. Allergic fungal sinusitis is an allergic reaction with degenerated eosinophils resulting in alternating tide-lines of degenerated inflammatory cells with Charcot-Leyden crystals and fungal hyphae [22]. In general, none of the fungal infections have a true

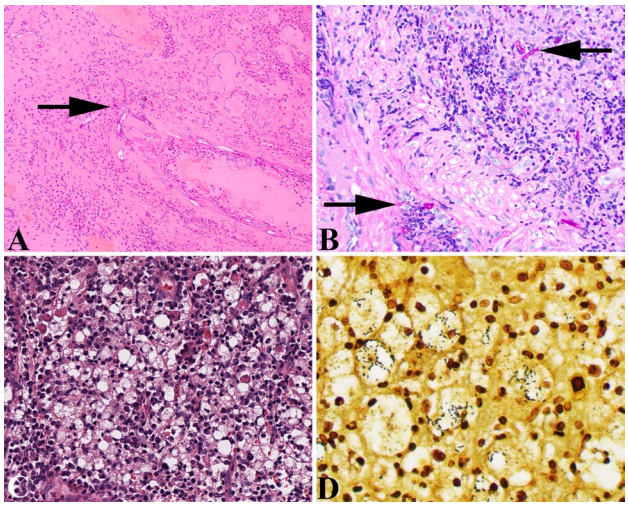

Fig. 4 **a** Invasive fungal sinusitis showing fungal hyphae (black arrow) within the vessel wall. **b** A PAS-Fungus control stain shows numerous fungal hyphae (black arrows) within the vessel wall and in the adjacent stroma. **c** Rhinoscleroma showing numerous plasma cells and many foamy histiocytes (called Mikülicz cells). **d** A Warthin-Starry stain highlights intracellular bacilli

fibroblastic reaction, but erosion or ulceration may result in reactive fibrosis.

Rhinoscleroma

Rhinoscleroma (sometimes called Hebra nose) is a rare, chronic infectious disease caused by *Klebsiella rhinoscleromatis*, a Gram-negative coccobacillus from the Enterobacteriaceae family, that affects the nasal cavity and nasopharynx [17, 23–25]. Young adults are most frequently affected, females more often than males, primarily in endemic regions, such as parts of South America, Central America, Africa, India, and Indonesia. There are three overlapping clinical phases: (a) rhinitic (ozena, catarrhal, exudative) stage characterized by a foul-smelling mucopurulent nasal discharge with nasal obstruction and erythema; (b) granulomatous (florid, proliferative) stage marked by mucosal thickening by numerous small masses and subsequent nasal obstruction; (c) scleroma (fibrotic, cicatrical) stage, characterized by marked scarring, tissue retraction, and nasal stenosis. MacConkey agar is used to grow the fastidious organism, but is only positive in about 50% of cases.

Grossly there are friable nasal polyps, which become more densely fibrotic with time. Rhinoscleroma is usually biopsied during the florid or fibrotic stage, where there is an expanded submucosa by an inflammatory infiltrate including lymphocytes, plasma cells, neutrophils, and histiocytes. Russell bodies (cytoplasmic inclusions of immunoglobulin) are frequent. The diagnostic histologic finding is "Mikülicz cells," large vacuolated histiocytes filled with organisms (Fig. 4c). Over time, the lesions become increasingly fibrotic and less inflammatory, sometimes showing vasculitis, pseudoepitheliomatous hyperplasia, and ulceration. A spindled component is generally absent [26, 27]. A Warthin-Starry stain highlights the encapsulated, nonmotile, rod-shaped Klebsiella bacilli within the Mikülicz cells (Fig. 4d), while immunohistochemistry for the capsular antigen 3 is highly specific and sensitive. Rosai-Dorfman shows emperipolesis of plasma cells or lymphocytes, a finding not seen in rhinoscleroma [28].

Mycobacterial Infections

Generally, mycobacterium infections include several species within the genus, with tuberculosis (*Mycobacterium tuberculosis*) and leprosy (*Mycobacterium leprae*) the most common considerations in the sinonasal tract, but also *Mycobacterium avium-intracellulare* for a mycobacterial spindle cell tumor [29, 30]. Infections caused by *Mycobacterium leprae* affect the cutaneous, mucosal, and peripheral nerves, with the cooler peripheral sites (such as digits, ears, and nose) commonly affected by the low infectivity organism. However, in the context of this discussion, it is the spindled cell tumor-like proliferation caused by mycobacterium avium complex that is considered. Nearly all of the patients are immunocompromised in some way, with human immunodeficiency virus (HIV) infected patients or patients receiving immunosuppressive therapy most commonly affected [29, 31]. There is no sex predilection, with a wide age affected, although frequently in young adults. A mass lesion is detected clinically, whether as lymph node enlargement, a subcutaneous nodule, or mucosal mass [29]. The nasal septum is most commonly affected [29, 30, 32].

The lesions are unencapsulated, partially to completely effacing the normal architecture by a proliferation of fibroblast-like spindle cells. The cellular proliferation is composed of bland-appearing, spindle-shaped cells in a haphazard to storiform pattern. The spindled cells have eosinophilic, granular appearing cytoplasm, as these facultative histiocytes phagocytose the infectious mycobacterial organisms (Fig. 5a). Isolated areas of necrosis may be seen, but in general a well-formed granuloma is not seen. Further, multinucleated giant cells and foamy histiocytes are generally focal or absent. A background of inflammatory cells, including lymphocytes and plasma cells are seen [30, 32]. A Ziehl-Neelsen stain will highlight innumerable intracytoplasmic bacilli (Fig. 5b), while fluorescence microscopy also identifies the organisms. Nuclei acid probes can be used to confirm the exact species [33]. Importantly, the histiocyte/macrophages are immunoreactive with CD68, lysozyme, S100 protein, and muscle specific actin [29, 31, 32], but CD31, CD34, ERG, FLI1, and HHV-8 are negative. Kaposi sarcoma may be concurrently present given the

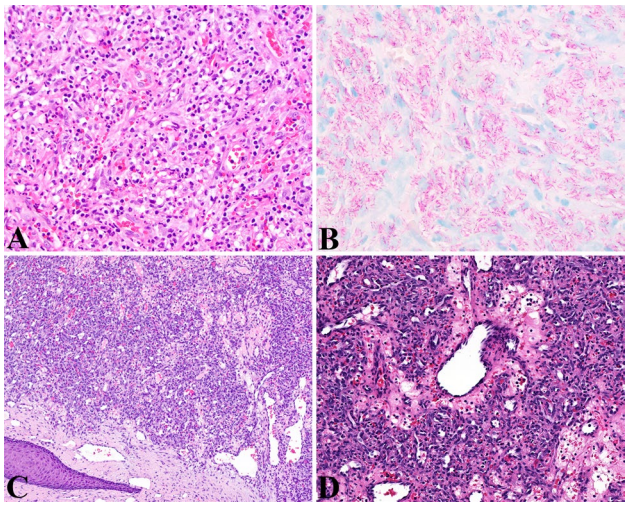

Fig. 5 **a** A mycobacterial spindle cell tumor shows a spindled cell population with numerous inflammatory cells. **b** An AFB stain reveals innumerable intracellular organisms within the histiocytes. **c** A lobular capillary hemangioma showing a subepithelial proliferation of vessels arranged in a lobular pattern. **d** There is a central vein surrounded by a cellular endothelial-lined proliferation of slit-like vessels

strong HIV-association, with a positive HHV-8 immunohistochemistry. Leiomyoma usually have more "box-like" nuclei, perinuclear vacuoles, and lack inflammation.

Neoplastic

Neoplasms of the upper aerodigestive tract frequently show a spindled morphology, with spindle cell squamous cell carcinoma and spindle cell melanoma the most frequent, while glomangiopericytoma, leiomyoma, peripheral nerve sheath tumors, solitary fibrous tumor, biphenotypic sinonasal sarcoma, leiomyosarcoma, and rhabdomyosarcoma are additional mesenchymal neoplasms to consider in this site. However, most of these lesions do not have a prominent inflammatory component associated with the neoplastic proliferation and so these tumors are not further discussed. However, several lesions may have an admixed fibroinflammatory population.

Lobular Capillary Hemangioma

Lobular capillary hemangioma is a benign capillary proliferation with a microscopically distinctive lobular architecture frequently with a friable surface, associated with a rich inflammatory infiltrate with a predilection to the oral cavity and sinonasal tract [34]. There is a difference in sexes based on age, with an initial peak in children (first decade) and adolescent males (male: female, 4:1), females in the reproductive years (especially when pregnant or taking oral contraceptives) (male: female, 1:4), and then an equal distribution beyond 40 years of age [35–37]. Patients present with unilateral epistaxis and/or an obstructive painless mass present for a short duration due to the urgent nature of the symptoms. The anterior septum (specifically the Little area) and the turbinate (usually anterior tip) are more commonly affected in the sinonasal tract than are the paranasal sinuses [38, 39].

Tumors often present as a polypoid (pedunculated) nodule, soft and compressible. A collarette of epithelium is often noted at the stalk or base, with secondary changes (ulceration, hemorrhage, thrombosis) frequent. There is a lobular, circumscribed anastomosing network of capillaries with plump endothelial cells and often a proliferation of pericytes in a fibromyxoid stroma arranged in one or more lobules (Fig. 5c). Each lobule is composed of a large central vein ("feeder" vessel) surrounded by aggregates of small variably sized capillaries with plump endothelial cells (Fig. 5d), with an overlying epithelium (often ulcerated or atrophic). The vessel lumina may be indistinct to slightly open, with the packed vessels surrounded by intact pericytes. Mitoses are invariably present but without atypical forms. If the mass is superficial in location, secondary, nonspecific changes may be present, such as a granulation-type tissue with numerous capillaries and venules disposed radially to the surface with a markedly edematous stroma containing mixed inflammatory cells (neutrophils, lymphocytes, plasma cells, mast cells) and extravasated erythrocytes. There is often an arc of development, with early lesions having a greater number of vessels and edema to a more fibrotic lesion with fewer vessels. However, granulation tissue does not have a lobular architecture. Bacillary angiomatosis is also a disorder seen more frequently in HIV-infected or immunocompromised patients, showing clusters of neutrophils and lymphocytes associated with the vascular proliferation, showing pleomorphic bacilli with a Warthin-Starry stain [40]. Angiosarcoma can be quite deceptively low grade, but generally displays a freely anastomosing network of atypical endothelial-lined spaces, frequently with atypical mitoses, destructive growth, and tumor necrosis [41].

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a neoplasm composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and/or eosinophils [42]. Up to 60% of tumors have an anaplastic lymphoma kinase (*ALK*) gene (2p23) rearrangement with a wide variety of fusion partners. There is a higher frequency of *ALK* rearrangements in children and young adults than in patients > 40 years of age at presentation [43], and within the head and neck, patients tend to be older than patients with tumors of other sites [42, 44–46]. For head and neck

IMT, there is no sex predilection. Symptoms are nonspecific. Within the sinonasal tract, the maxillary sinus is most commonly affected [46].

Tumors are identified below the surface epithelium, which may be ulcerated. Bone invasion may be seen, while lymphovascular or perineural invasion is uncommon. There is no circumscription or encapsulation. The spindled myofibroblastic cells are loosely arranged, showing a vague storiform or cartwheel architecture (Fig. 6a). The cells are spindled, stellate, slightly plump epithelioid to gangliocytic in appearance, set within a myxoid, loose background stroma rich with inflammatory cells (lymphocytes, plasma cells, neutrophils, eosinophils). Axonal or spider-like ganglion cells with eccentric nuclei can usually be detected (Fig. 6b). There is vesicular, open nuclear chromatin, small nucleoli, and frequent intranuclear cytoplasmic inclusions. There is often a fibrillar quality to the cytoplasm. Occasional tumors are more cellular with compact fascicles of spindled cells and a more collagenized stroma. Histiocytes, including multinucleated forms, may be seen. Three main histological patterns are recognized: myxoid, hypercellular, and hypocellular patterns, suggested to be a chronologic progression [47, 48]. About 60% of head and neck IMTs, especially in patients < 40 years of age, show ALK immunoreactivity, a finding that correlates with *ALK* gene rearrangements, and the pattern of reactivity matching gene fusions [43, 49]. The spindled cells also show a focal to patchy, weak to strong reactivity for SMA, MSA, calponin, and desmin, with focal keratin reactivity seen in up to 30% of cases [48]. IgG and IgG_4-positive plasma cells may be seen, the latter raising consideration for IgG_4-related disease [50–52]. Desmoid-type fibromatosis has more of a purposeful direction to the collagen, little to no inflammation, and shows a strong nuclear ß-catenin reaction with a negative ALK.

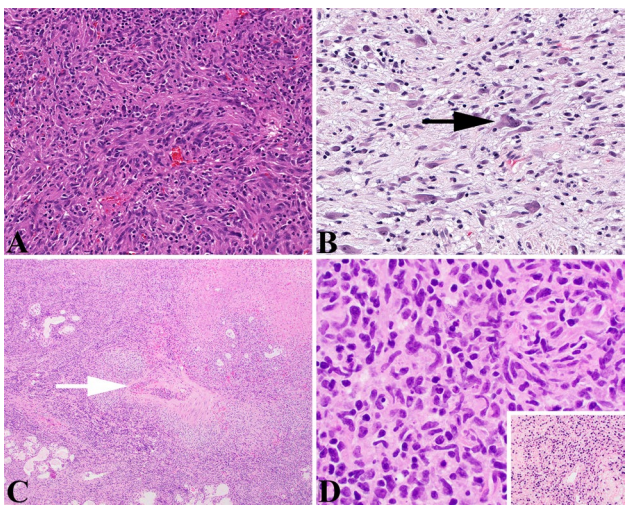

Fig. 6 **a** An inflammatory myofibroblastic tumor (IMT) shows a haphazard spindled cell proliferation associated with a mixed inflammatory infiltrate. **b** A hypocellular IMT with several ganglion-like myofibroblasts (black arrow). **c** A low power of an extranodal NK/T-cell lymphoma, nasal type (ENKL) with areas of necrosis and angiodestruction (white arrow). **d** High power of an ENKL showing remarkably atypical and convoluted cells, highlighted by a strong nuclear EBER (dark blue nuclei; inset)

Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is extranodal when it develops in the sinonasal tract and is a lymphoma of mature NK-cell or T-cell lineage showing angiocentric destruction with prominent tumor cell necrosis, a cytotoxic phenotype, and a near constant association with Epstein-Barr virus (EBV), irrespective of ethnicity [53]. In endemic regions (such as East Asia, Central and Latin America), ENKL accounts for about 15% of all lymphomas [53, 54]. ENKL develops over a wide age range (1–83 years) but tends to be seen most often in younger adults (mean age at presentation: 35–45 years), with males affected more commonly than females by a 2.4:1 ratio [53–55]. Initial symptoms are non-specific, with swelling, nasal obstruction, difficulty breathing, and erythema, but with disease progression, extensive mid-facial destruction develops with associated epistaxis, pain, and paresthesia. Importantly, more than one biopsy is often required, which results in delay in diagnosis [56]. Ulceration, necrosis, nasal septal destruction, and palatal perforation or destruction are common.

Epithelial ulceration is common, occasionally associated with pseudoepitheliomatous hyperplasia during healing [57]. Epitheliotropism is also noted, with micro-abscesses of neoplastic cells seen in the epithelium. Angiocentric and angiodestructive growth are nearly always present (Fig. 6c), with atypical cells seen within the vessel walls associated with fibrinoid degeneration of the walls and/or fibrin thrombi within the vessels. Extensive, geographic, coagulative, ischemic-type necrosis results. Minor mucoserous glands are destroyed by the infiltrate, and thus appear reduced in number. There is a very broad cytomorphologic appearance, usually related to an arc of development. A reactive inflammatory background includes lymphocytes, plasma cells, histiocytes, and eosinophils with medium- to large cells that show nuclear pleomorphism, irregular, folded, and elongated nuclei, coarse granular chromatin, and moderate cytoplasm (Fig. 6d)[58]. Mitoses are easily identified and include atypical forms. Multinucleated giant cells and granulomas are usually absent. Elastic stains may aid in identifying angiodestruction. The neoplastic cells are usually positive with CD2, CD56, and cytoplasmic CD3-epsilon and negative with CD5. EBV is universally expressed, detected with in situ hybridization for EBV-encoded small RNA (EBER; Fig. 6d, inset) [59, 60]. There is variable reactivity with CD43, CD45RO (UCHL1), CK7, and p53 while negative

with CD4, CD8, CD16, and CD57 [61, 62]. In about 30% of cases, a T-cell lineage is present, demonstrating cytotoxic T-cell granules, identified by positive immunoreactions with granzyme B, TIA1, and/or perforin, along with CD5, CD8, and T-cell receptors (gamma delta or alpha beta) [63–65]. While a large number of lesions are in the differential, nearly all are negative with EBER, which can be a very useful guide in diagnosis.

Conclusions

Even though there is wide diversity in the fibroinflammatory category of sinonasal tract lesions, a systematic approach based on general categories (reactive, infectious, neoplastic) and proceeding from the most common to the rare, will allow for appropriate diagnosis utilizing selected ancillary techniques.

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Compliance with Ethical Standards

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Conflict of interest The author declares he has no conflict of interest as it relates to this review.

Ethical Approval This review article was performed in accordance with ethical standards and did not require informed consent. The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of Southern California Permanente Medical Group.

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