Sino-Nasal Sarcoidosis

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Case Presentation 1

DW was a 41-year-old black female when she developed eye pain and was found to have anterior uveitis. As part of her evaluation, she had a chest X-ray which demonstrated bilateral hilar adenopathy and diffuse lung filtrates. She was diagnosed as having sarcoidosis on clinical grounds. She was not dyspneic and denied cough. Her iritis was treated with topical steroids and within 6 months she was tapered off steroid drops.

She then started having recurrent sinus symptoms. Initially this was felt to be allergic rhinitis and she was treated with intranasal steroids. Three years later, she developed severe pain behind and below her right eye. She underwent an MRI and was found to have complete opacification of her right maxillary sinus (Fig. 13.1a, b). She was seen by an ophthalmologist, who diagnosed her as having dacrocystitis, with compression of her nasolacrimal duct. She first had surgical intervention to clear her ethmoid and maxillary sinuses. Pathologic examination of the surgical specimen revealed non-caseating granulomas. After recovery, a nasolacrimal stent was placed by her ophthalmologist. Confirmation of placement of the stent beyond the inflammation was made by the otolaryngologist in the operating room.

Postoperatively the patient was placed on prednisone 40 mg a day. Over the next 6 months, attempts to reduce the dose below 20 mg a day led to recurrence of pain and bleeding from her sinuses. She was started on methotrexate and after 6 months she was able to reduce her prednisone to 10 mg a day.

Two years later, she began having recurrent sinus infections. These usually responded to antibiotics and prolonged courses of high-dose prednisone. She developed macular papular lesions on her cheeks and nasal alae. She also had new papular lesions on her arms. A biopsy of one of the arm lesions again found granulomas consistent with sarcoidosis.

She was felt to have refractory sarcoidosis with sinus disease and *lupus pernio*. The antitumor necrosis factor (TNF) antibody infliximab was initiated. The patient received 5 mg/kg initially, then 2 weeks later, and then once a month. She has done well on the combination of infliximab, methotrexate, and low-dose prednisone. She has been maintained on 5 mg-a-day prednisone and has not required increased prednisone for more than a year.

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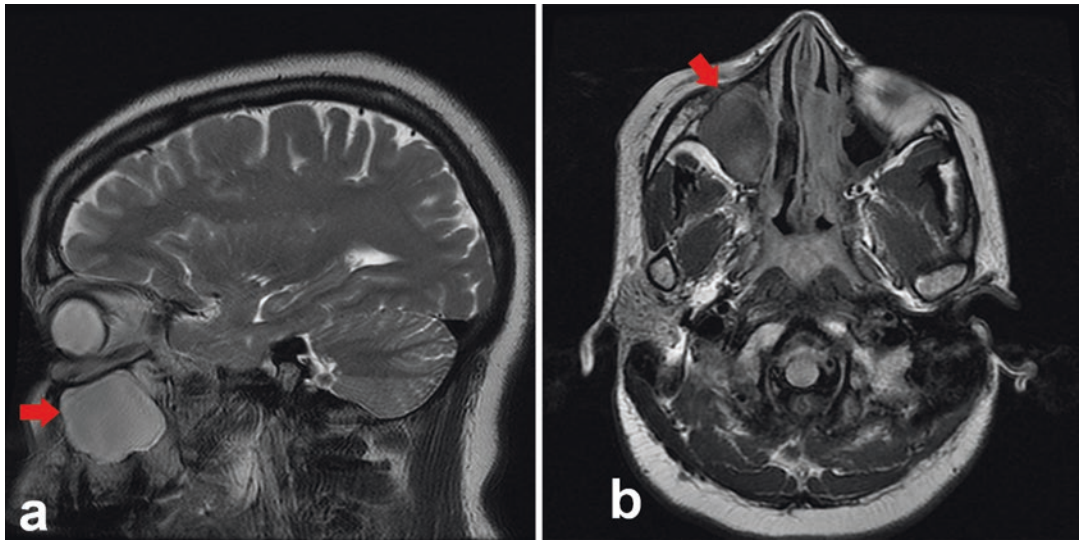

Fig. 13.1 MRI imaging demonstrating right ethmoid opacification (arrow). (**a**) Sagittal view. (**b**) Axial plane

Case Presentation 2

MC is a black female who at the age of 39 was complaining of sinus congestion and a sore on the roof of her mouth. She was referred to an otolaryngologist because of refractory sinus disease. He noted on exam that her hard palate was perforated. She denied cocaine or other drug use. A sinus biopsy found non-caseating granulomas. Her antineutrophil cytoplasmic antibody (ANCA) test was repeatedly negative. She was referred to our sarcoidosis clinic. On exam, she was noted to have extensive purplish, raised lesions of the entire nose. She also had lesions on both cheeks and was diagnosed as having *lupus pernio*. Her chest X-ray demonstrated upper lobe fibrosis consistent with Scadding stage 4 sarcoidosis. She was initially treated with prednisone and methotrexate with only modest response.

Because of insurance issues, she was not seen for 3 years. She was referred back to clinic because of respiratory distress. She had been taken off her methotrexate for unclear reasons and was on only 5 mg-a-day prednisone when she had developed acute stridor. She was found to have recurrence of pan sinusitis (Fig. 13.2a) as well as laryngeal infiltration and upper airway narrowing (Fig. 13.2b) by what proved to be her sarcoidosis. She was only marginally better on 40 mg prednisone.

She was then started on adalimumab since her insurance would not cover infliximab. After 3 months, she started improving and eventually she was weaned to 10 mg-a-day prednisone and maintained on adalimumab 40 mg weekly.

After 2 years, she developed left hip and upper leg pain. On MRI, she was found to have an infiltrative lesion. A percutaneous needle aspirate of the bone lesion was consistent with a low-grade liposarcoma. She had surgical resection of the lesion. Because of concerns about potential carcinogenicity of adalimumab, the drug was discontinued.

Over the next 2 years, she has had no evidence of recurrence of her tumor. However, her sinus disease and facial lesions returned within 3 months of stopping the adalimumab. She was initially controlled with prednisone alone. However, as she gained more weight with the prednisone, she asked for another steroid-sparing regimen. She was begun on repository corticotrophin injection (RCI) 40 units twice. For the past year, she has been maintained on RCI alone, that with no oral prednisone.

Comments on two cases: Both of these cases had sinus disease and *lupus pernio.* This skin lesion is highly specific for sarcoidosis. It is also

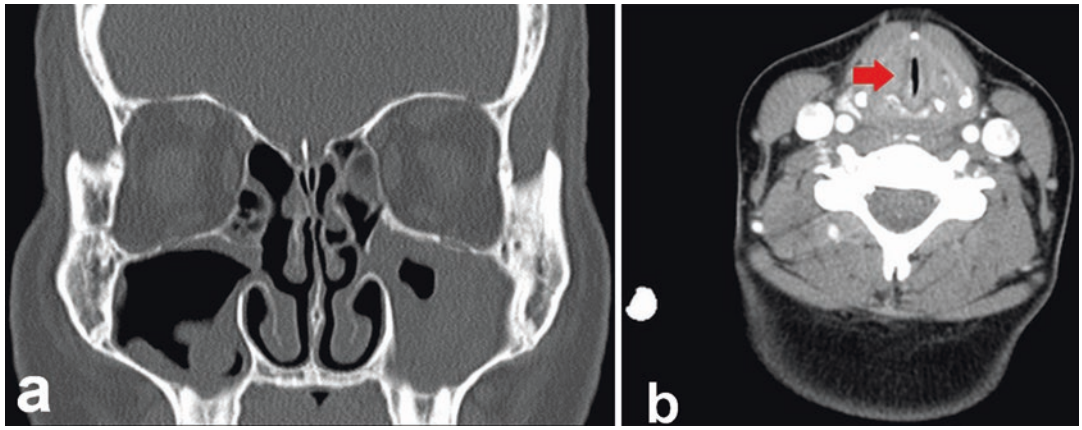

Fig. 13.2 CT scan coronal plane of sarcoidosis patient. (**a**) Sinus disease and retention cyst. (**b**) Upper airway narrowing (arrow)

commonly associated with sinus sarcoidosis. In some series of *lupus pernio*, around half of the patients had symptomatic sarcoidosis of the sinus [1, 2]. Dacrocystis is another condition associated with sinus sarcoidosis. In sarcoidosis patients with dacrocystitis, stenting alone is unlikely to work. That is because there is a high risk for granulomatous reaction to the stent. In case one, immunosuppressive therapy was able to control the disease. Both of these cases had refractory disease requiring third-line therapy. Anti-TNF antibodies can be quite effective in chronic conditions, including *lupus pernio* [3]. Unfortunately, the second case developed a liposarcoma while receiving were adalimumab. The patient is currently stable on another third-line treatment, RCI.

General Discussion

Sino-nasal sarcoidosis is one of the many manifestations of sarcoidosis of the upper respiratory tract (SURT) [4, 5]. Nasal and sino-nasal disease is the most common manifestation of SURT, but the larynx, oral cavity, and tongue can also be affected [5, 6]. Sinus symptoms are common in sarcoidosis patients. In one prospective study, nearly 40% of patients complained of nasal symptoms that had lasted for more than 3 weeks [7]. Half of these patients continued to have symptoms despite nasal steroids and short-course antibiotic therapy. However, biopsy confirmation of sino-nasal sarcoidosis was made in only 4% of all patients in the study.

Etiology and Epidemiology of Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology [8]. The defining feature of sarcoidosis is the granuloma. One proposed model of sarcoidosis is exposure to an antigen, usually through inhalation [9]. This antigen activates several cells including macrophages and dendritic cells through the Toll-like receptor-2 (TLR-2). The dendritic cell transports the antigen across the epithelium to the lymph node, where it is processed with differentiation and clonal expression of T helper cells (Th1 and Th17). The antigen also stimulates macrophages to release tumor necrosis factor (TNF). TNF crosses the epithelial layer where it activates tissue macrophages and natural killer (NK) cells. Stimulated NK cells release interferon gamma (IFN-γ) which upregulates the tissue macrophages. The activated macrophages and clonal Th1/Th17 cells form the core of the granuloma. Other cells in the granuloma include T regulatory cells (Treg) and B cells (B cells). Key cytokines involved in the

granuloma formation include MCP-1, CCL20, and CXCL10.

For most sarcoidosis patients, the granuloma resolves over the first few years. However, persistence of granulomas leads to chronic disease. Several features have been associated with persistent granulomas. The most important may be the upregulation of Th17.1 cells [10, 11], programmed death cells (PD-1) [12], and Treg cells [13]. Certain cytokines have been associated with chronic disease, including CXCL9 [14] and interleukin 8 (IL-8) [15, 16]. Persistent production of TNF by alveolar macrophages has also been found in patients with chronic sarcoidosis [17]. These observations have led to treatment strategies focused on these potential targets.

The antigen which stimulates the inflammatory response of sarcoidosis remains unknown. Several potential ligands for TL2-R have been studied. Antibodies for mycobacterial proteins mKatG [18], ESAT-6 [19], and *M. tuberculosis* heat-shock proteins (Mtb-hsp) [20] have been reported in a significant number of sarcoidosis patients, mostly from North America. However, no studies to date have been able to identify mycobacteria that are causing the antibody reaction. Studies from Japan and China have found evidence for propionibacterium including *P. acnes* in over half of the cases they studied [21, 22]. Inhaled particles have also been reported to cause a sarcoidosis-like reaction. Some first responders to the World Trade Center attack developed a sarcoidosis-like reaction, including multi-organ disease [23]. These observations support the hypothesis that sarcoidosis is due to multiple antigens. What makes sarcoidosis sarcoidosis is the reaction to the antigen(s) (Fig. 13.3).

Sarcoidosis is a worldwide disease. Table 13.1 summarizes the estimated incidence and prevalence of sarcoidosis for some countries across the world [24–26]. In the United Sates, several studies have noted that the disease is more frequent in African-American women [25, 27, 28]. Figure 13.4 demonstrates the prevalence rate per 100,000 population for African-American and Caucasian women and men in one recent study of over thirty-two million Americans [25]. In this study, sarcoidosis was more frequently observed in women than men for all races studied, including Asian and Hispanics.

Clinical Presentation and Diagnosis of Sino-Nasal Sarcoidosis

Nasal congestion is the most common feature in patients with sino-nasal sarcoidosis [5, 29, 30]. In a prospective study of 159 sarcoidosis patients, 60 (38%) had nasal symptoms (usually congestion) for at least 3 weeks [7]. Twenty-seven still had symptoms after 3 weeks of nasal steroids and oral antibiotics. Of these, six were found to have biopsy-confirmed sino-nasal sarcoidosis. Epistaxis was noted in 10–30% of cases [5, 29, 30]. In one series of 12 cases of biopsy-confirmed sino-nasal sarcoidosis, anosmia was noted in five, crusting in eight, and polyps in four cases [29]. Other areas in the upper airway can be involved in sino-nasal sarcoidosis. These include the larynx, oral cavity, and tongue [5, 6].

At the University of Cincinnati Sarcoidosis clinic, we have seen 2000 patients with sarcoidosis in the past 6 years. Of these, 64 (3.2%) had sino-nasal sarcoidosis. This was the most common manifestation of SURT in our clinic, with an additional 39 patients having upper airway or parotid involvement without documented sino-nasal disease. Table 13.2 summarizes the clinical features and the frequency of other organ involvement, using standard organ involvement criteria [31]. Patients with sino-nasal involvement were younger at the time of diagnosis of sarcoidosis than those without sino-nasal involvement. There was no difference in the race or gender for those with or without sino-nasal involvement. Lung and eye involvement were reported with equal frequency in both groups. Skin involvement was more common in those with sino-nasal disease, often on the face (Fig. 13.5a). In this group, 20% of patients with sino-nasal disease had *lupus pernio* (Fig. 13.5b).

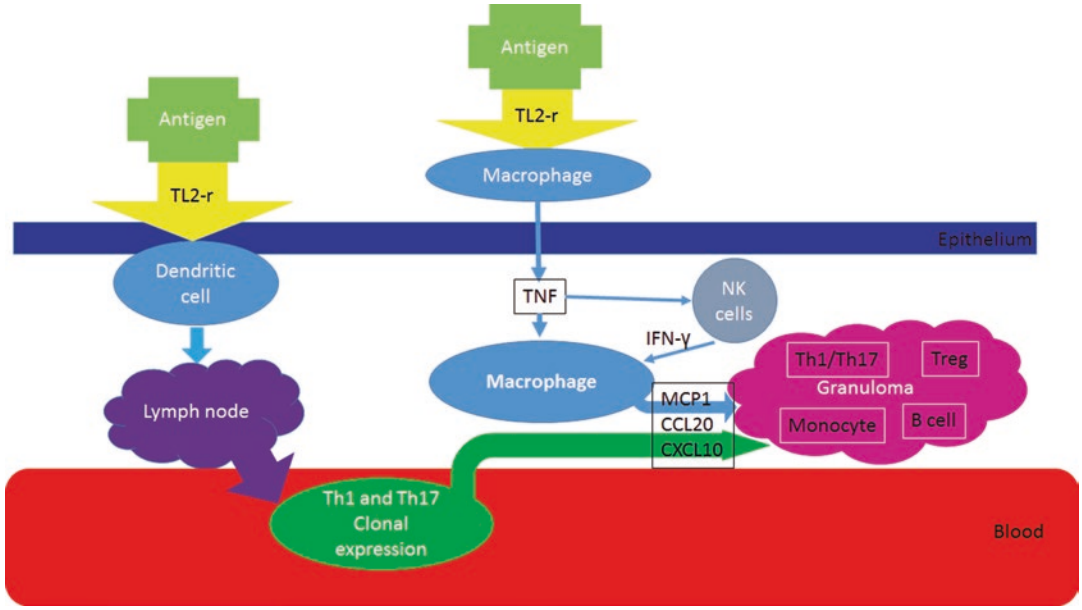

Fig. 13.3 Inhaled antigen comes into contact with cells at the epithelial layer. Activation of both macrophages and dendritic cells occurs through the Toll-like receptor-2 (TLR-2). The dendritic cell transports the antigen across the epithelium to the lymph node, where it is processed and differentiation and clonal expression of T helper cells (Th1 and Th17) occur. The antigen also stimulates macrophages on the surface of the epithelium and leads to the release of tumor necrosis factor (TNF). TNF crosses epithelial layer where it activates tissue macrophages and natural killer (NK) cells. NK releases interferon-gamma (IFN-γ) which upregulates the tissue macrophages. The activated macrophages and clonal Th1/Th17 cells form the core of the granuloma. Other cells in the granuloma include T regulatory cells (Treg) and B cells (B cells). Key cytokines involved in the granuloma formation include MCP-1, CCL20, and CXCL10

Table 13.1 Estimated incidence and prevalence of sarcoidosis[a]

Country	Population (millions)	Incidence per 100,000	Total new cases per year	Prevalence per 100,000	Total cases
China[a]	1312	0.56	7349	2.1	27,190
India[a]	1131	4.57	51,669	16.9	191,176
United States[b]	247[c]	8.8	21,736	60	148,200
Japan[a]	127	1.3	1657	4.7	5990
Germany[a]	82	4	3118	14	11,537
France[a]	61	3	1649	10	6101
United Kingdom[a]	60	5	4000	27	16,270
Sweden[d]	8[c]	11.5	920	160	12,800

[a]Estimated by Denning et al. [24]
[b]Reported by Baughman et al. [25]
[c]Only for those aged 18 or older
[d]Reported by Arkema et al. [26]

Diagnosis of Sino-Nasal Sarcoidosis

Many patients with documented sino-nasal sarcoidosis have been diagnosed prior to the diagnosis of sino-nasal involvement. Sarcoidosis patients present with a wide range of symptoms, including no symptoms at all. In up to a third of cases, patients are detected based on an abnormal chest X-ray or laboratory test [32]. Symptoms from sarcoidosis depend on what organ is affected. Table 13.3 summarizes the symptoms,

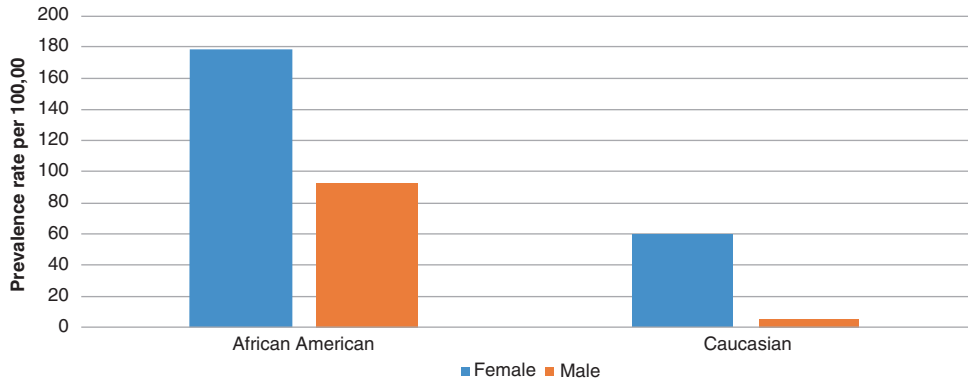

Fig. 13.4 Prevalence rate for sarcoidosis in the United States for African-Americans and Caucasians. Higher rate observed for female versus male for both races [25]

Table 13.2 Clinical features of sino-nasal sarcoidosis at University of Cincinnati sarcoidosis clinic

Feature	Number
Total number	64 (3.2%)[a]
Age at the time of diagnosis, years (median [range])	37 (21–60)[b]
Female:male	46:17
African-American:Caucasian	34:28
Lung involvement	58 (90.6%)[c]
Skin involvement	38 (59.4%)[d]
Lupus pernio	13 (20.3%)[e]
Eye involvement	24 (37.5%)
Other upper airway involvement	
Larynx	1
Parotid	2
Tongue	1
Supraglottic	1

[a]Of a total of 2000 patients seen in clinic
[b]Significantly younger than sarcoidosis patients without sino-nasal involvement ($p = 0.0001$)
[c]Percent of all sino-nasal sarcoidosis cases
[d]Skin involvement significantly more frequent than sarcoidosis patients without sino-nasal involvement (Chi square = 34.4, $p < 0.0001$)
[e]Lupus pernio significantly more frequent than sarcoidosis patients without sino-nasal involvement (Chi square = 63.5, $p < 0.0001$)

physical findings, and laboratory tests for various manifestations of the disease. Criteria have been established for identifying various organ involvement [33].

Criteria have also been developed to define sino-nasal involvement in sarcoidosis [33]. A patient with known sarcoidosis elsewhere who has granulomatous changes on direct fiber-optic nasal endoscopy or imaging studies (Fig. 13.6) is felt to have at least probable sino-nasal sarcoidosis. Patients with chronic sinusitis are felt to have at least possible sino-nasal sarcoidosis. Patients with a positive sinus or nasal biopsy demonstrating non-caseating granulomas are highly probable to have sino-nasal sarcoidosis.

Patients with sino-nasal sarcoidosis can have a range of symptoms, including no specific complaints [5, 30, 34], although nasal congestion and rhinorrhea are reported in most cases. Crusting and/or epistaxis occur in about a quarter of patients. Anosmia, purulent rhinorrhea, and facial pain can also occur. Local examination will often demonstrate hypertrophy and/or a purplish hue due to the granulomatous inflammation. Figure 13.6 shows an endoscopic view of a patient with sino-nasal sarcoidosis.

Figure 13.7 shows our approach to evaluation of patients with possible sino-nasal disease [7]. Patients with nasal congestion or other symptoms are treated with nasal steroids and/or antibiotics. If symptoms persist for more than 3 weeks, a CT scan is performed. If the scan is suggestive of sinus disease, the patient is considered for referral to an otolaryngologist for possible endoscopy and biopsy. If the CT scan is normal, the patient may receive a longer course of therapy. If the

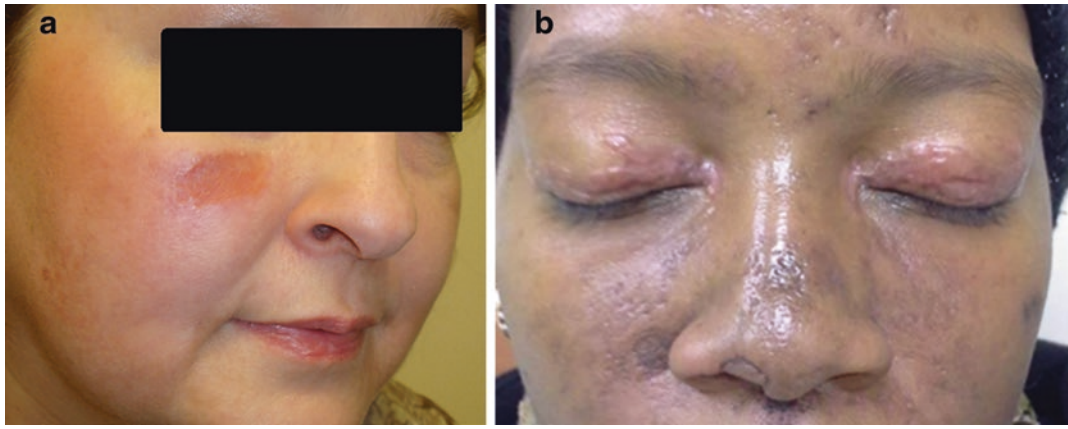

Fig. 13.5 Sarcoidosis lesions of patients with sino-nasal sarcoidosis. (**a**) Lesion on cheek. (**b**) Nasal and periocular lesion of patient with *lupus pernio*. Both patients provided written informed consent for publication of their photographs

Table 13.3 Common symptoms, physical findings, and laboratory tests in sarcoidosis

	Symptom	Physical finding	Laboratory test
Lung	Cough	Hilar adenopathy	Hilar adenopathy
	Dyspnea	Symmetrical upper lobe disease	Symmetrical upper lobe disease
	Chest pain	Peribronchial thickening on CT scan	Peribronchial thickening on CT scan
	Wheezing		Restriction and/or obstruction on PFTs
Eye	Pain	Iritis	Reduced visual fields
	Photophobia	Pars planitis	
	Blindness	Optic neuritis	
Neuro	Seventh cranial nerve paralysis		Gadolinium enhancement on MRI
	Unilateral weakness		Lymphocytic meningitis
	Seizure		
Cardiac	Palpitations		Ventricular arrhythmias
	Edema		Complete heart block
			Reduced left ventricular ejection fraction
			Late gadolinium enhancement on cardiac MRI
			Patchy enhanced uptake of cardiac PET scan
Skin	Lesions on face, arms, legs	Macular papular lesion	
		Lupus pernio	
		Papules in areas of scarring or tattoos	
Liver	Abdominal pain	Enlarged liver and/or spleen	Hepato/splenomegaly on imaging
Others			Increased serum or urine calcium with elevated vitamin D 1,25
			Elevated ACE level

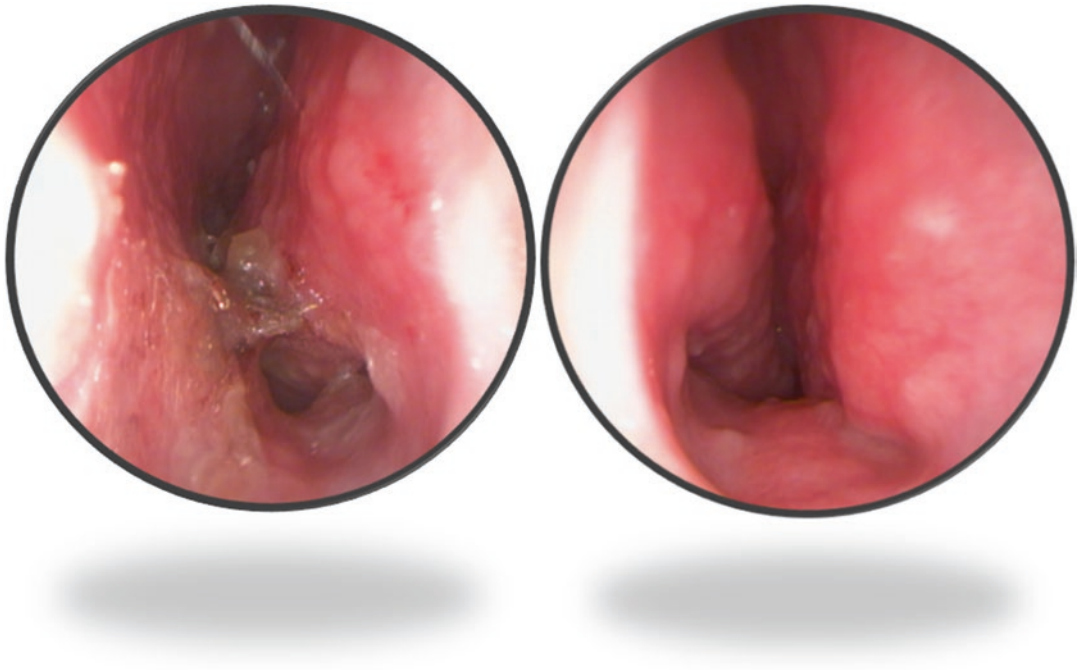

Fig. 13.6 Nasal endoscopic view of a patient with sino-nasal sarcoid. Submucosal nodules are evident on the nasal septum and inferior turbinate, and even the nasal floor

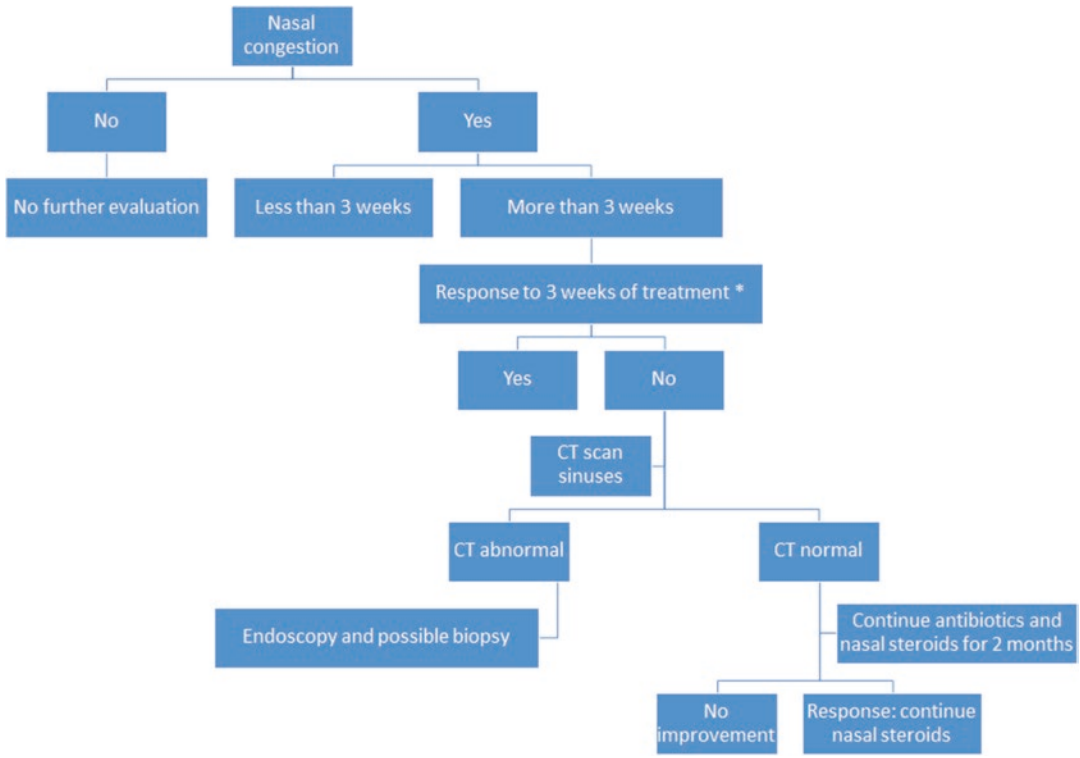

Fig. 13.7 University of Cincinnati Sarcoidosis Clinic approach to evaluation of patients with possible sino-nasal disease [7]. *Treatment with nasal steroids and/or oral antibiotics

patient is still requiring therapy after 2 months, they are referred for evaluation.

CT scanning is the most common imaging modality to detect sino-nasal disease, with abnormalities seen in most cases [30, 34]. Mucosal hypertrophy and/or opacification occurs in almost all cases of sino-nasal involvement. Turbinate or septal nodularity is present in about a third of cases (see Fig. 13.6), and bone lesions including erosions and osteoneogenesis is present in over a third of cases [30, 34].

There are some additional features that heighten the likelihood of sino-nasal sarcoidosis. *Lupus pernio* are papular lesions on the cheeks and nose, especially the nares [35]. In general, lupus pernio is seen in less than 2% of all sarcoidosis patients [36]. It is more frequent in patients of African descent, but can be seen in Caucasians [2, 3, 35]. There is strong association between *lupus pernio* and sino-nasal disease [1, 2].

Another important association is dacrocystitis. The drainage of the tear duct into the sinus can be blocked and lead to significant morbidity. This can be treated surgically with a dacryocystorhinostomy, although recurrent obstruction may occur [37]. Patients with dacrocystitis often have adnexal lesions [38]. In these patients, a CT scan may demonstrate lacrimal gland involvement as well as significant sinus disease (Fig. 13.8).

Table 13.4 lists the differential diagnosis of granulomatous sinus disease. In addition to routine pathologic examination, special stains should be performed to look for evidence of lymphoma or infection. In addition, testing for antineutrophil cytoplasmic antibody (ANCA) should be performed. Further characterization of ANCA should be done to distinguish between cytoplasmic (c-ANCA) and perinuclear (p-ANCA). Systemic granulomatosis disease with polyangiitis (GPA), formerly known as Wegener's disease, is strongly associated with a positive c-ANCA. On the other hand, a positive p-ANCA test has been reported in various inflammatory diseases, including Churg-Strauss.

The serum angiotensin-converting enzyme (ACE) has limited sensitivity and specificity in part because of genetic polymorphisms of the ACE enzyme [39] and because of the effect of corticosteroid therapy [40] on levels. However, a significantly elevated ACE level can be helpful in confirming the diagnosis of sarcoidosis. Over half of patients with active sarcoidosis will have an ACE level greater than 20% of the upper limit of normal. Patients with an ACE level that high have a greater than 90% chance of having sarcoidosis [41].

Management

The management of sino-nasal disease is usually a stepwise process. Figure 13.9 is the approach we employ in management of patients at our clinic. Initial therapy is topical, with use of nasal corticosteroids to control inflammation. If that is unsuccessful, we will use oral corticosteroids, usually prednisone.

In general, oral corticosteroid therapy for sarcoidosis is a long-standing intervention. Short-course treatments of up to 3 weeks are reserved for acute events [42, 43]. The rationale for long-term treatment with corticosteroids is because of the high rate of relapse of sarcoidosis when treatment is withdrawn [5, 30]. Once systemic therapy is initiated for sarcoidosis, about half of patients will require systemic therapy for more than 2 years [44, 45]. Some features, such as *lupus pernio*, are associated with the need for systemic treatment for 5 years or longer [46]. The goal with oral corticosteroid therapy is to reduce the patient to the lowest possible dose that maintains a clinical remission [47]. For most sarcoidosis patients, a maintenance dose of prednisone of less than 10 mg daily or its equivalent is associated with minimal adverse effects and is generally well tolerated [48].

For those patients unable to tolerate maintenance-dose prednisone or who have progressive disease despite corticosteroid therapy, antimetabolite therapy is a steroid-sparing alternative. Methotrexate is the most widely studied and used treatment as a second-line therapy for sarcoidosis [25, 49]. Table 13.5 summarizes several reported series as well as our own experience

with various systemic therapies to treat sinonasal sarcoidosis. For most studies, methotrexate was the most widely used steroid-sparing agent. Table 13.6 compares the various systemic treatments for sarcoidosis, including dosage and toxicity. Specific recommendations have been made for administrating and monitoring methotrexate therapy in sarcoidosis patients [50]. Azathioprine and leflunomide have been used less frequently to treat sarcoidosis. However, these drugs appear to be about as effective as methotrexate [51–53]. Mycophenolate has recently been reported as an effective steroid-sparing agent in sarcoidosis [54, 55]. All four of these agents seem to work about two-thirds of the time as steroid sparing. The use of an individual agent depends on the experience of the clinician and potential or real toxicity for the individual patient.

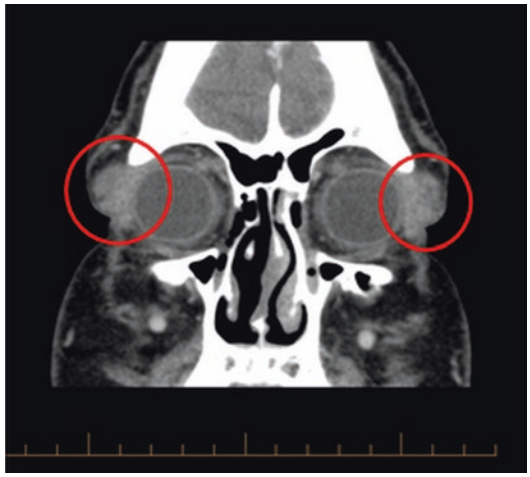

Fig. 13.8 Coronal CT scan demonstrating bilateral lacrimal gland involvement (red circles) in a sarcoidosis patient with dacrocystitis who also has left maxillary sinus disease

The antimalarial drugs hydroxychloroquine and chloroquine appear to be most effective for treatment of cutaneous disease [56]. They are not as effective for more aggressive forms of sarcoidosis, such as *lupus pernio* [3]. For sinonasal sarcoidosis, they are often used as an adjunct to other treatments (see Table 13.5). Their toxicity is relatively low, although patients need to undergo routine ocular screening [57].

Monoclonal antibodies to tumor necrosis factor (anti-TNF) have changed the outcome of many patients with chronic sarcoidosis. Infliximab, a chimeric monoclonal antibody, has been the most widely used anti-TNF drug. In advanced pulmonary sarcoidosis, it was found to be significantly better than placebo treatment [58]. It was also found to be more likely to induce complete resolution of *lupus pernio* than any other drug combination [3]. Adalimumab has also been reported as effective in treating sarcoidosis, including *lupus pernio* [59, 60]. Not all

Table 13.4 Differential diagnosis of sino-nasal disease[a]

Disease	Differentiating features	Comments
Sarcoidosis	Multi-organ disease	Elevated ACE
Infectious rhinitis	Positive culture and/or special stains	Actinomycosis, Aspergillosis, Blastomycosis, Histoplasmosis, Mucomycosis, leprosy, syphilis
Granulomatosis with polyangiitis	Necrotizing vasculitis, associated with lung and renal disease	ANCA positive, especially c-ANCA
Churg-Strauss syndrome	Necrotizing granulomas with vasculitis, bronchial asthma, eosinophilia	ANCA positive, especially p-ANCA
Polymorphic reticulosis	Angiocentric lymphoid infiltrate	
Berylliosis	Non-caseating granulomas limited to lung, skin, and sinuses	Positive beryllium lymphocyte stimulation test Exposure to beryllium
Tuberculosis	Caseating granulomas	Positive smears and culture for *M. tuberculosis*
Lymphoma	Immunohistochemistry demonstrating clonal B or T cell infiltration	

[a]Adapted from Zeitlin et al. [7]

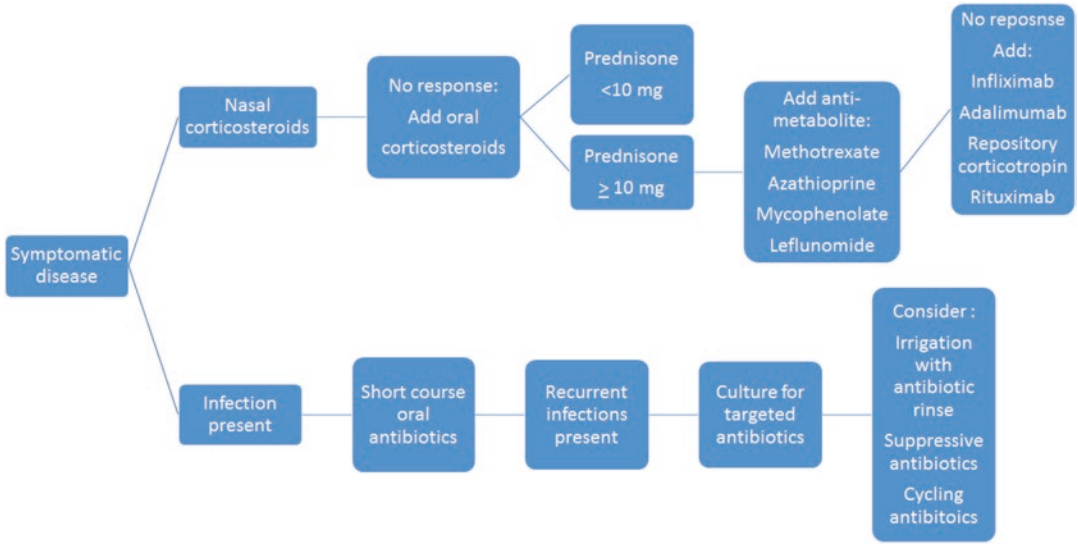

Fig. 13.9 A stepwise approach to management of sino-nasal sarcoidosis. Treatment is for the underlying sarcoidosis (top half of the flowchart) as well as management of any infection. Prednisone is the most commonly used oral corticosteroid in our clinic. Surgical management of residual scarring is usually reserved until after inflammation is controlled

Table 13.5 Systemic therapy for sino-nasal sarcoidosis

	University of Cincinnati Sarcoidosis Clinic 2016	Aloulah et al. (2013) [34]	Kirsten et al. (2013) [29]	Aubart et al. (2006) [30]	Zeitlin et al. (2000) [7]
Number of patients	64	38	12	20	18
No therapy	4	14	0	0 [b]	0
Prednisone [a]	60	24	12	18	13
Methotrexate	52	NC	NC	8	13
Azathioprine	12	NC	NC	2	3
Leflunomide	15	NC	NC	0	0
Mycophenolate	2	NC	NC	0	0
Hydroxychloroquine/ chloroquine	16	NC	NC	14	4
Infliximab	16	NC	NC	0	0
Adalimumab	2	NC	NC	0	0
Rituximab	2	NC	NC	0	0
Repository corticotrophin	7	NC	NC	0	0
Surgery[c]	NC	4	1	7	4

NC no comment
[a]Patients may have received more than one treatment
[b]Other treatments include thalidomide, cyclophosphamide, pentoxifylline, and cyclosporine
[c]Excludes biopsy

anti-TNF agents are equally effective in treating sarcoidosis. Adalimumab appears to be less potent than infliximab [61]. A recent randomized trial failed to demonstrate a benefit of golimumab versus placebo [62]. Moreover, these drugs are associated with significant potential toxicity. Guidelines have been developed for use of these drugs in patients with sarcoidosis [63].

Rituximab is a monoclonal antibody against B cells. While originally developed to treat lym-

Table 13.6 Systemic therapy for sarcoidosis

Drug	Dosage	Estimated efficacy (%)	Recommended monitoring	Common/significant toxicity
Prednisone	Initial 20–40 mg daily Maintenance 5–10 mg daily	>90	Glucose, blood pressure, edema, osteoporosis	Toxicity is dose dependant
Methotrexate	5–15 mg weekly	60	CBC, liver, renal function every 2–3 months	Bone marrow suppression, nausea, hepatotoxicity up to 5%, rarely pulmonary toxicity
Azathioprine	50–200 g daily	60	CBC, liver, renal function every 2–3 months	Bone marrow suppression, nausea, rarely hepatotoxic
Mycophenolate	500–1500 twice a day	50	CBC every 2–3 months	Bloating, diarrhea
Leflunomide	10–20 mg daily	60	CBC, liver, renal function every 2–3 months	Bone marrow suppression, less nausea, hepatotoxicity up to 5%, very rare pulmonary toxicity, peripheral neuropathy
Hydroxychloroquine	200–400 mg daily	20	Eye examination every 6–12 months	Rarely heart block, dermatitis, hepatotoxicity
Infliximab	3–5 mg/kg initially, 2 weeks later than once every 4–6 weeks	85	Initial screening for latent tuberculosis, monitor for fungal infections	Allergic reactions including anaphylaxis, reactivation of tuberculosis, dermatitis, lupus-like reaction, skin cancer, worsening congestive heart failure, solid malignancy, lymphoma, demyelinating diseases
Adalimumab	40 mg every 1–2 weeks	80	Initial screening for latent tuberculosis, monitor for fungal infections	Less likely allergic reactions than infliximab, reactivation of tuberculosis, dermatitis, lupus-like reaction, skin cancer, worsening congestive heart failure, solid malignancy, lymphoma, demyelinating diseases
Rituximab	1000 mg initially, 2 weeks later and then maintenance every 1–6 months	70	Screen for prior viral infections, including hepatitis B and C, monitor immunoglobulin levels every 3–6 months	Reaction to infusion, viral infections, IgG deficiency
Repository corticotrophin injection	40–80 units twice a week	50–80	Glucose, blood pressure, edema, osteoporosis	Toxicity is usually on the day of injection, edema and increased anxiety are frequent, toxicity is dose dependant

phoma, it has been found to have significant immunomodulatory effects. The drug has been reported as effective in refractory pulmonary [64] and ocular [65] disease.

Repository corticotrophin injections (RCI) have recently been reported as effective in treating advanced sarcoidosis [66]. While an old therapy, it had been abandoned for many years in routine management of sarcoidosis because of cost and question of mechanism of action. The drug stimulated the melanocortin receptors (MCR), including MCR-2. The

MCR-2 is on the adrenal gland and stimulation leads to release of cortisol. However, there are several other MCRs, including some that regulate the immune system. Stimulation of these other MCR is felt to have benefit beyond just steroid effect of the drug [67]. Repository corticotrophin injection has been used in cases of refractory sarcoidosis who have failed conventional therapy and/or developed significant toxicity to various treatments [68].

Most patients with sarcoidosis can be managed medically [34]. As noted in Table 13.5, surgical intervention has been used in the management of sino-nasal sarcoidosis [29, 69]. While some cases may respond to surgery [69], relapses after surgery are common [7, 29, 30]. Endoscopic surgery may be effective in controlling symptoms [70], but it can be very difficult to control healing and prevent scarring. The risk for relapse can be reduced by aggressive use of immunosuppressive agents. However, immunosuppression will only reduce inflammation and has no impact on scar tissue. Once scarring occurs, surgery may prove effective in removing obstruction. Even extensive reconstruction surgery has been successfully performed when inflammation has been controlled [71].

Lawson et al. have proposed the classification of sino-nasal sarcoidosis as atrophic, hypertrophic, destructive, and nasal enlargement [72]. They reported good results with surgery only for the subgroup of patients with architectural changes. While these recommendations seem reasonable, they were based on a retrospective review of a limited number of cases and need to be confirmed prospectively.

For the therapy of sino-nasal sarcoidosis, one has to also consider infection. Abnormal sinus architecture from sarcoidosis represents the same challenge for the clinician as any other condition which affects the sinuses. Antibiotic regimens often progress in a stepwise fashion as depicted on the bottom half of Fig. 13.9 [73]. Cultures may provide evidence to support targeted therapy, especially for aspergillosis and atypical mycobacteria. Figure 13.10 demonstrates the CT scan of a patient with chronic ocular, pulmonary, and sinus sarcoidosis treated at our institution. While on infliximab and methotrexate therapy, she had developed a chronic sinus infection. Cultures of her left maxillary sinus grew *M. avium*. Her sinus symptoms responded well to withdrawal of infliximab and anti-mycobacterial therapy. However, she had to be placed back on prednisone 20 mg to control her ocular disease.

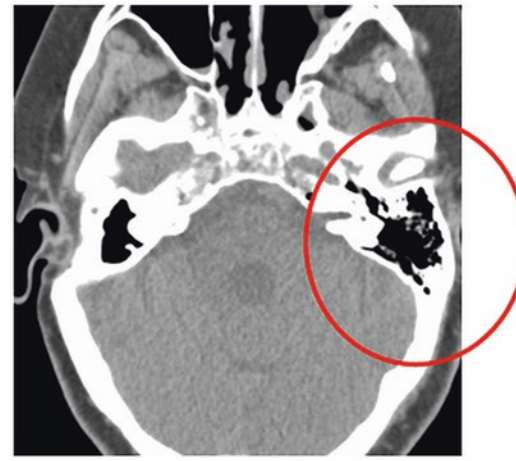

Fig. 13.10 Axial CT scan of head of a 70-year-old white female with chronic ocular, pulmonary, and sinus sarcoidosis for more than 12 years. Patient had developed headache and fever while on maintenance therapy of methotrexate 10 mg a week and infliximab 5 mg/kg once a month. Her CT scan demonstrated fluid collection in left maxillary sinus. Biopsy of sinus showed highly cellular inflammation with numerous acid-fast bacilli seen on special staining. Culture grew *M. avium* complex (MAC). Her infliximab was discontinued and she was placed on anti-mycobacterial therapy. While her sinus symptoms resolved, her optic neuritis flared and prednisone was reinstituted. After 1 year of anti-mycobacterial therapy, she is stable and without evidence of mycobacterial infection. However, she remains on 20 mg prednisone daily with 10 mg-a-week methotrexate

In addition to targeted antibiotic therapy, nasal rinses with broad-spectrum antibiotics can be utilized. Gentamicin is commonly used, since topical application usually does not lead to toxicity. However, systemic absorption can still occur [74] and toxicity should be assessed for those on chronic therapy. Prolonged use of systemic antibiotics has shown benefit in some patients [75]. However, these antibiotic regimens have not been studied in sino-nasal sarcoidosis.

Conclusion

While sino-nasal sarcoidosis is an unusual form of sarcoidosis, it often leads to chronic disease. For some patients, local therapy may be sufficient. Systemic therapy follows a stepwise approach, with prednisone or similar oral corticosteroid the initial drug of choice. However, because of the need for long-term therapy, steroid-sparing alternatives should be considered early in the management of advanced sino-nasal disease. Antimetabolites are effective steroid-sparing agents. Newer modalities, including anti-TNF antibodies, have proved effective in treating refractory cases. Surgery is effective in addressing architectural changes due to scarring. It is most effective in patients in whom inflammation is controlled by immunosuppression therapy.

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