European Archives of Oto-Rhino-Laryngology (2019) 276:1969–1974
https://doi.org/10.1007/s00405-019-05388-7

RHINOLOGY

Sarcoidosis of the paranasal sinuses

Thorsten Send[1] · Izabela Tuleta[3] · Tim Koppen[1] · Thore Thiesler[4] · Klaus W. Eichhorn[1] · Mattis Bertlich[2] · Friedrich Bootz[1] · Mark Jakob[2,5]

Received: 28 February 2019 / Accepted: 12 March 2019 / Published online: 21 March 2019

Abstract

Background Sarcoidosis is a chronic disease, which predominantly affects the lung. Since sinonasal sarcoidosis is rare, little is known about the sarcoidosis manifestation at this site. Therefore, the aim of our study was to detect the prevalence of sinonasal sarcoidosis, its clinical occurrence, diagnosis, and therapy.

Methods The database of all patients having visited the otorhinolaryngology departments of the universities in Göttingen and in Bonn between 2003 and 2016 was searched for the diagnosis of sinonasal sarcoidosis.

Results Thirteen patients with a biopsy-proven sinonasal sarcoidosis were identified. Most patients presented non-specific clinical symptoms, which are also found in acute and chronic sinusitis. None of the patients was suspected to have sinonasal sarcoidosis by the ENT doctor before histological validation. The mean diagnostic delay was 262 (±195) days. An additional pulmonary involvement was detected in four of six patients.

Conclusions Sinonasal sarcoidosis is presenting with heterogeneous clinical presentations. An early biopsy of granulomatous lesions is mandatory. A multidisciplinary approach is needed to exclude serious lung or heart manifestations, because even asymptomatic organ involvement is possible. A CT-scan may be useful even if unspecific. Local or systemic therapy has to be prepared individually using local and systemic corticosteroids, antimetabolites, or anti-TNF-alpha.

Keywords Sarcoidosis · Granulomatous disease · Extrapulmonary sarcoidosis · Sinonasal sarcoidosis · Paranasal sinus

Introduction

Sarcoidosis is a chronic non-caseating granulomatous disease of unknown origin and was first described in 1877 [1, 2]. It is a multisystem disease which can affect any organ and has a prevalence of 5–50 per 100,000 [1, 3–5]. The most common manifestation with up to 90% is the lower respiratory tract with enlarged intrathoracic lymph nodes or pulmonary parenchymal infiltrates [2]. About 10–30% of all patients with sarcoidosis present a head and neck manifestation [6, 7]. Only limited data are available regarding the frequency of sinonasal sarcoidosis. In the literature, the incidence has been estimated between 0.7% and 6.0% [8–11]. Environmental, infectious, and genetic and immune factors may trigger the development and progression of this disease [12].

Clinical symptoms

Since sinonasal sarcoidosis is not common and because of its non-specific symptoms, which often resemble classic signs of acute or chronic sinusitis (e.g., rhinitis, headache, chronic inflammatory rhinosinusitis, epistaxis, anosmia, facial pain, crustation, or nasal obstruction), finding the right diagnosis can be challenging [7, 14, 15]. On the way to a correct diagnosis, a poor response to conventional treatment is typical [1]. The systemic progression of the disease varies widely and ranges from a mild, self-limited illness to a fulminant,

✉ Thorsten Send
thorsten.send@ukbonn.de

1 Department of Otorhinolaryngology, Head and Neck Surgery, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany

2 Department of Otorhinolaryngology, Munich University (LMU), Munich, Germany

3 Department of Internal Medicine-Cardiology, University of Munster, Munster, Germany

4 Department of Pathology, University of Bonn, Bonn, Germany

5 Department of Otorhinolaryngology, University of Goettingen, Göttingen, Germany

widespread multisystem organ involvement [13]. Common non-specific symptoms of systemic sarcoidosis can be fatigue, weight loss, fever, hemoptysis, shortness of breath, or other pulmonary symptoms [13].

Local diagnostic

In case of granulomatous lesions, a biopsy is needed to exclude other diseases (Gold Standard), such as tuberculosis, Wegener granulomatosis, fungal infection (e.g., aspergillosis and actinomycosis), Churg–Strauss syndrome, syphilis, or lepromatous leprosy (Table 1) [8, 17–19]. If a biopsy is not possible, you have to find your diagnosis by exclusion. Histopathological investigation reveals a granulomatous disease with typical Langhans giant cells and epithelioid cells (Fig. 2) [13]. Usually, concomitant pulmonary and extrapulmonary sarcoidosis can be detected in patients with a biopsy-proven sinonasal lesion, whereas an isolated manifestation in the sinonasal area is rare [17].

Systemic diagnostic

Due to the fact that the major cause of death in patients with sarcoidosis lies in the systemic involvement of cardiac, respiratory, neurological, or hepatic manifestations, the multisystemic disease must be excluded during further diagnostic procedure [30]. A chest X-ray or high-resolution computed tomography for a better detection should be undertaken to examine the pulmonary tissue for potential sarcoidosis-associated alterations, e.g., enlarged mediastinal lymph nodes or scars [20, 21]. Furthermore, lung function testing and a bronchoscopy with bronchoalveolar lavage to determine whether the CD4/CD8 ratio is higher than 3.5 (sensitivity 53%, specificity 94%) and whether the angiotensin-converting enzyme blood levels are elevated may be useful (Table 2) [21–23]. Nevertheless, there are no specific serological markers for the diagnosis and monitoring of the disease, but angiotensin-converting enzyme (ACE) and Interleucin-2 receptor (IL-2) are used as activity markers in patients with systemic sarcoidosis [30].

Local therapy

The therapy focuses on the reduction of systemic inflammation (Fig. 3) [24]. Some authors recommend topical nasal steroids, decongestants, and periodic antibiotics after a multisystem disease has been excluded and if the disease is limited to the nose or paranasal sinuses [13, 15].

Systemic therapy

First-line therapy in severe cases or patients with systemic manifestation consists of oral systemic steroids. Systemic steroids are very effective and particularly important when critical organs are involved (Fig. 3) [13, 25].

As a second-line therapy, if topical or systemic steroids are not effective or there are contraindications for their use,

Table 1 Granulomatous sinonasal diseases as a differential diagnosis

Infectious: tuberculosis, syphilis, leprosy, actinomycosis, rhinoscleroma, fungal diseases (e.g., aspergillosis)
Autoimmune: Wegener's granulomatosis, Churg–Strauss syndrome, Behcet
Idiopathic: sarcoidosis
Secondary granulomas: rheumatoid arthritis and systemic lupus erythematosus

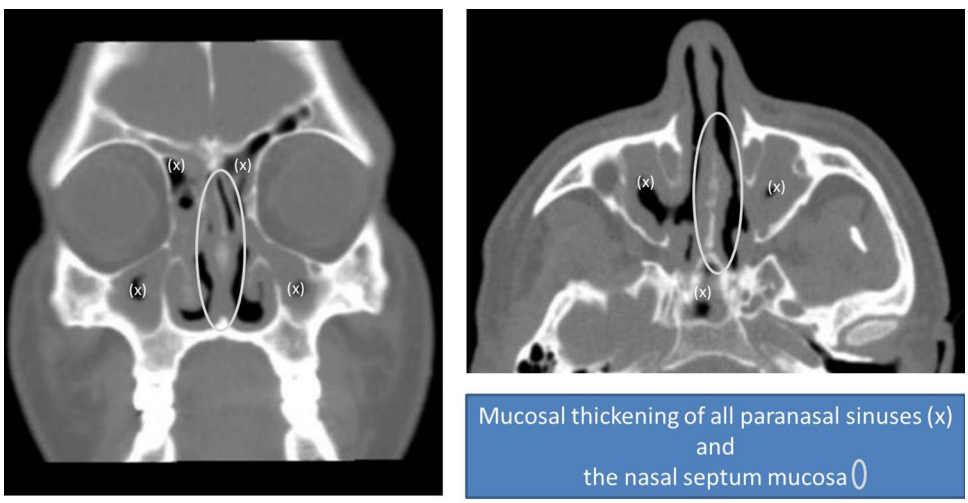

Fig. 1 Computed tomography of paranasal sinus sarcoidosis (coronal/sagittal)

Table 2 Diagnostic screening procedure for multi-organ involvement (modified from: Prasse [1] and Aleksoniene et al. [2])

Standard diagnostic
General physical examination
Radiology
Chest X-ray
Computer tomography (CT) of the chest (optional, superior)
Ultrasound sonography of the abdomen
Magnetic resonance imaging (MRI) of CNS (optional if suspected)
Positron emission tomography (18F-FDG-PET) (optional if bone involvement suspected)
Pulmonary function test
Echocardiography
Bloodtest
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Alkaline phosphatase (AP)
Gamma-glutamyl transferase (gamma-GT)
Calcium
Creatinine
Quantiferon test (interferon-release assay)
Urine test
Calcium
Creatinine

cytotoxic and immunomodulating agents may be considered [26].

Third-line therapy comprises anti-TNFα therapy (e.g., infliximab, adalimumab, etanercept, and golimumab), which has proved to be an effective treatment for refractory disease and may improve the outcome of most patients. However, there are still non-responders [27, 28].

Surgical therapy

The role of surgical interventions as a therapy is questionable because of the high risk of relapse which is why they should only be considered in severe cases or to control local symptoms, even if the intervention itself is safe [15].

Materials and methods

We investigated all patients of the otorhinolaryngology departments of two university hospitals in Göttingen and in Bonn. Sarcoidosis patients were identified based on the ICD-10 (International Statistical Classification of Diseases and Related Health Problems) admission diagnosis for sarcoidosis (D86) and on a full-text search of all discharge letters (keyword: sarcoidosis). Patient files as well as the electronic documentation system were used to obtain the data of each individual patient. For the 13-year period between 2003 and 2016, we found 13 patients with biopsy-proven sinonasal sarcoidosis and retrospectively analyzed these patients by evaluating the respective medical files containing clinical symptoms, histology reports, and treatment regimens.

Ethical considerations: In this retrospective study, no patient-identifying data in accordance with German law were used.

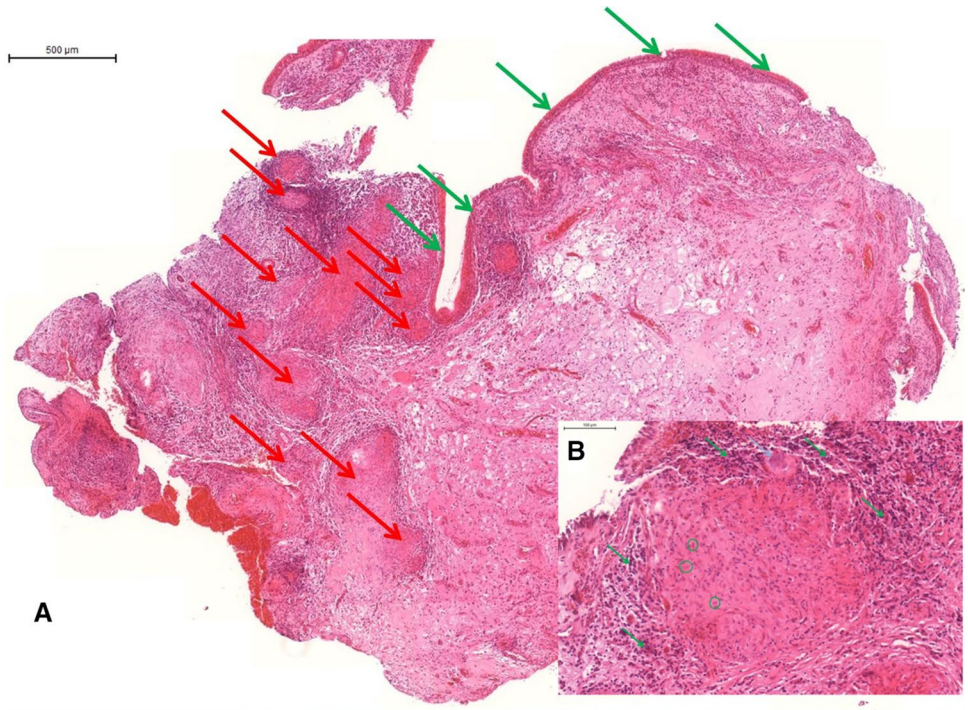

Fig. 2 Histopathology example of sarcoidosis. **a** Pseudostratified respiratory mucosa (green arrow) with multiple well-formed non-caseating granulomas (red arrow). Hematoxylin–eosin, ×35 magnification. **b** The granulomas consist of tightly clustered aggregates of epithelioid histiocytes (green circle) with a surrounding rim of lymphocytes (green arrow). Intermixed with the histiocytes are scattered multinucleated giant cells (blue arrow). Hematoxylin–eosin, ×200 magnification

Results

Between 2003 and 2016, 13 patients with paranasal sarcoidosis, verified by biopsy, were identified in two university hospitals. Six of these patients were treated at the Otorhinolaryngology Department of the University Hospital Göttingen and seven patients at the Otorhinolaryngology Department of the University Hospital Bonn. Overall, six patients were male. The average age at the time of the first validation of the sarcoidosis diagnosis by biopsy was 48.77 ± 12.72 years (median 52.5 years).

Most patients with paranasal sarcoidosis showed clinical symptoms of sinusitis of the affected nasal sinus (84.62%, $n = 11$) with nasal breathing disorders (46%, $n = 6$), rhinorrhea, anosmia, and throat pain or swelling (7.69%, $n = 1$). Another cardinal symptom was a symptomatic eye or nasolacrimal duct involvement with, for example, epiphora (23.08%, $n = 3$). With only one exception, the localization of the sarcoidosis in the nasal sinuses was limited to the ethmoid cells and the maxillary sinuses. A strict unilateral or bilateral manifestation could not be shown. The diagnosis of sinonasal sarcoidosis was not suspected by the ENT doctor before the surgical intervention in any of the presented cases. In 15.38% ($n = 2$) of patients, however, the manifestation of sarcoidosis in other organ systems was previously known, which means that the primary diagnosis of sarcoidosis came from the ENT doctor in all remaining cases (84.62%, $n = 11$). The mean diagnostic delay was more than 262 ± 195 days (median 339 days). Six (54.55%) of the recently diagnosed patients were transferred to the Department of Pneumology for further examinations and hematological testing. Four (36.36%) of them received an initial therapy with systemic oral corticosteroids following the detection of pulmonary involvement by performing X-ray, pulmonary function testing, or bronchoscopy (Table 3). Computer tomography showed pathologically suspicious cervical, mediastinal, or hilar lymph nodes for all of these patients ($n = 4$). Two of them additionally presented pulmonary infiltration.

The cardiac and rheumatic status data were not fully collected, but we can assume a multisystemic appearance in more than 46% of the cases ($n \geq 6$).

Discussion

Up to 30% of all patients with sarcoidosis have head and neck manifestations [6, 14, 29]. Isolated sarcoidosis which exclusively affects the sinonasal tract is rare and nasal involvement occurs in approximately 1% of all patients suffering from this disease [31, 32]. Nevertheless, we were able to identify 13 patients with the diagnosis of paranasal sarcoidosis in our two-center study. In the literature, very few data are available regarding frequency and clinical characteristics and only small cohort studies are described in

Table 3 Patients with oral steroid therapy due to lung involvement

Patient	Lung involvement	Therapy
1	Lung involvement stadium II (CT and chest X-ray) Positive hematological results ACE (134 U/l) ESR (1 h 50+, 2 h 85+) CRP (6.6 mg/l) Hypergammaglobulinemia	Local nasal steroids and Oral steroids 30 mg per day for 4 week stepwise reduction to 7.5 mg per day for 6 month withdrawal trial after 6–12 month
2	Lung involvement stadium I (CT and chest X-ray) Positive initial hematological results IL-2 (740 U/l) CRP (3.7 mg/l) ACE normal Negative hematological results (after 4 weeks therapy) IL-2 normal (300 mg/l) ACE normal (21 U/l)	Local nasal steroids and Oral steroids 40 mg per day for 4 weeks, 30 mg per day 2 weeks, 25 mg per day 2 weeks, and 20 mg per stepwise reduction to 7.5 mg per day withdrawal trial after 6–12 months
3	Lung involvement stadium I (CT and chest X-ray) Negative hematological results	Local nasal steroids and Oral steroids 30 mg per day 2 weeks, 25 mg per day 2 weeks, and 20 mg per day until next visit
4	Lung involvement stadium I (CT and chest X-ray) Positive hematological results CRP (6,7 mg/l) ACE (102 U/l) IL-2 normal	Local nasal steroids and Oral steroids 40 mg per day 4 weeks, 30 mg per day 4 weeks, and 20 mg per day stepwise reduction to 7.5 m per day

ACE angiotensin-converting enzyme, *ESR* erythrocyte sedimentation rate, *CRP* c-reactive protein, *IL-2* interleukin 2 receptor

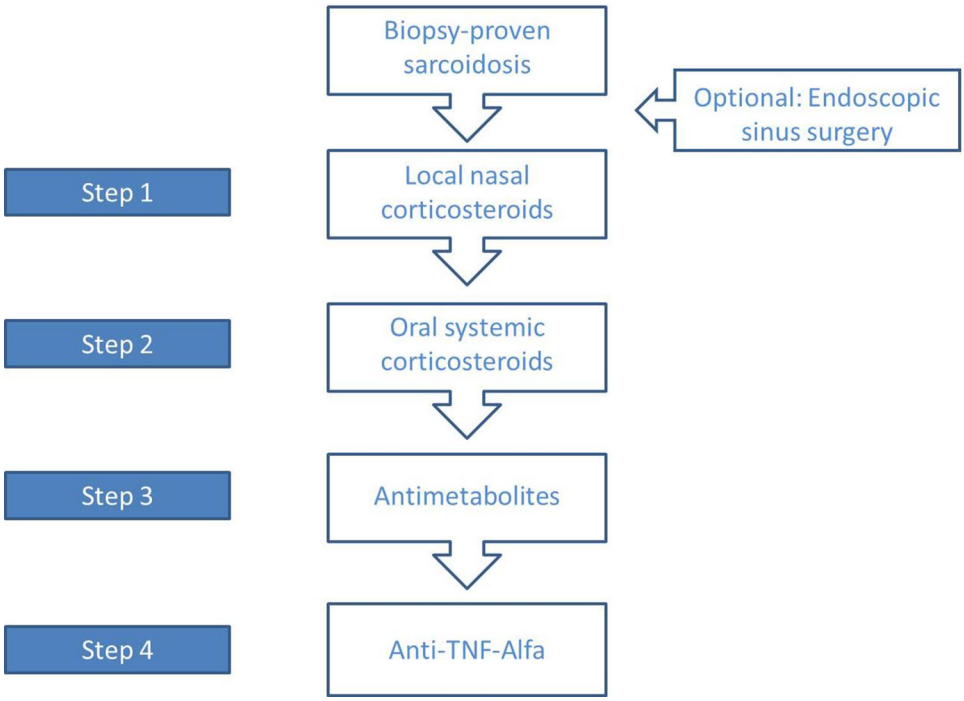

Fig. 3 Therapy pathway of paranasal sinus and systemic sarcoidosis

systematic reviews [1, 13, 33]. Even sarcoidosis self-help groups asked for more research and better education of students and physicians on this field and more interdisciplinary contacts [34].

All patients in this study had rhinorrhea or nasal obstruction. According to Lawson et al., there are four clinical patterns of the disease: mucosal hypertrophy, mucosal atrophy, nasal destruction, and nasal enlargement [16]. In our patients, we could not find any suspect evidence for sarcoidosis during clinical examination. Only two of our patients had a previous diagnosis of pulmonary sarcoidosis, but, even in these two cases, the pre-surgical diagnosis was chronic sinusitis, not sarcoidosis. This results from the fact that it is difficult for the ENT doctor to distinguish between sarcoidosis of the paranasal sinuses and common acute or chronic sinusitis.

Showing mucosal thickening, obstruction of the ostiomeatal unit or other sinuses, CT or MRI scans alone are non-specific for sinonasal sarcoidosis and not suitable to differentiate between sarcoidosis and paranasal infections (Fig. 1) [35]. Kirsten at al. noticed a predominance of opacification of both maxillary sinuses [14].

Although there are no standard diagnostic procedures and clear guidelines are lacking, the gold standard for the diagnosis of sinonasal sarcoidosis is a biopsy of sinonasal mucosa with histological evidence of epithelioid cell granulomas [10]. If there is a suspect lesion in the anterior nose, it is possible to take the biopsy in local anesthesia. We would recommend general anesthesia for a better overview of all paranasal sinuses, to get bigger tissue fragments or to biopsy multiple locations. In our clinic, we investigate every tissue and histopathological examination is standard, even if some studies suggest that such a routine examination has a little clinical value, if any at all [36]. Furthermore, differential diagnoses, such as Wegener's granulomatosis or tuberculosis, have to be excluded (Table 1) [13, 32].

Altogether, sarcoidosis of the paranasal sinuses is a relatively rare, but chronic disease and heterogeneous clinical presentations make a diagnosis of sinonasal sarcoidosis challenging. Furthermore, sarcoidosis with multisystemic symptoms can be a potentially life-threatening. The clinical diagnosis might be challenging due to non-specific symptoms. Based on the fact that sarcoidosis can affect every organ (e.g., lung and heart), a multidisciplinary approach is essential to prevent further complications. A higher level of awareness for sarcoidosis in case of suspicious granulomatous lesions may increase the detection rates of sinonasal sarcoidosis.

Funding No financial or material support.

Compliance with ethical standards

Conflict of interest No potential conflicts for all authors.

References

1. Braun JJ, Gentine A, Pauli G (2004) Sinonasal sarcoidosis: review and report of fifteen cases. Laryngoscope 114(11):1960–1963. https://doi.org/10.1097/01.mlg.0000147928.06390.db

2. Helliwell TR (2016) Non-infectious inflammatory lesions of the sinonasal tract. Head Neck Pathol 10(1):32–39. https://doi.org/10.1007/s12105-016-0689-6
3. Semenzato G (2005) ACCESS: a case control etiologic study of sarcoidosis. Sarcoidosis Vasc Diffus lung Dis 22(2):83–86. http://www.ncbi.nlm.nih.gov/pubmed/16053022. Accessed 3 May 2017
4. Scharkoff T (1993) Epidemiology of sarcoidosis. Pneumologie 47(10):588–592. http://www.ncbi.nlm.nih.gov/pubmed/8259367. Accessed 5 May 2017
5. Tuleta I, Skowasch D, Biener L et al (2017) Impaired vascular function in sarcoidosis patients. Springer, Cham, pp 1–9. https://doi.org/10.1007/5584_2016_203
6. Hofauer B, Chaker A, Thürmel K, Knopf A (2017) Manifestationen von Autoimmunerkrankungen in der HNO-Heilkunde. HNO 65(8):695–708. https://doi.org/10.1007/s00106-017-0380-6
7. Badhey AK, Kadakia S, Carrau RL, Iacob C, Khorsandi A (2015) Sarcoidosis of the head and neck. Head Neck Pathol 9(2):260–268. https://doi.org/10.1007/s12105-014-0568-y
8. Aubart FC, Ouayoun M, Brauner M et al (2006) Sinonasal involvement in sarcoidosis. Medicine (Baltimore) 85(6):365–371. https://doi.org/10.1097/01.md.0000236955.79966.07
9. Baughman RP, Lower EE, Tami T (2010) Upper airway.4: sarcoidosis of the upper respiratory tract (SURT). Thorax 65(2):181–186. https://doi.org/10.1136/thx.2008.112896
10. Colden D, Busaba NY (2000) Sarcoidosis presenting as recurrent nasal polyps. Otolaryngol Head Neck Surg 123(4):519–521. https://doi.org/10.1067/mhn.2000.106193
11. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, Kawabata Y (2017) Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. Acta Pathol Jpn 43(7–8):372–376. http://www.ncbi.nlm.nih.gov/pubmed/8372682. Accessed 3 May 2017
12. Adrianto I, Lin CP, Hale JJ et al (2012) Genome-Wide Association Study of African and European Americans Implicates Multiple Shared and Ethnic Specific Loci in Sarcoidosis Susceptibility. Perry JRB, ed. PLoS One 7(8):e43907. https://doi.org/10.1371/journal.pone.0043907
13. Krespi YP, Kuriloff DB, Aner M (2016) Sarcoidosis of the sinonasal tract: a new staging system. Otolaryngol Head Neck Surg. https://doi.org/10.1016/S0194-59989570240-7
14. Kirsten A-M, Watz H, Kirsten D (2013) Sarcoidosis with involvement of the paranasal sinuses—a retrospective analysis of 12 biopsy-proven cases. BMC Pulm Med 13(1):59. https://doi.org/10.1186/1471-2466-13-59
15. MARKS SC, GOODMAN RS (1998) Surgical management of nasal and sinus sarcoidosis. Otolaryngol Head Neck Surg 118(6):856–858. https://doi.org/10.1016/S0194-5998(98)70282-7
16. Lawson W, Jiang N, Cheng J (2014) Sinonasal sarcoidosis: a new system of classification acting as a guide to diagnosis and treatment. Am J Rhinol Allergy 28(4):317–322. https://doi.org/10.2500/ajra.2014.28.4061
17. deShazo RD, O'Brien MM, Justice WK, Pitcock J (1999) Diagnostic criteria for sarcoidosis of the sinuses. J Allergy Clin Immunol 103(5 Pt 1):789–795. http://www.ncbi.nlm.nih.gov/pubmed/10329811. Accessed 4 May 2017
18. Shah R, Roberson GH, Curé JK (2009) Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. AJNR Am J Neuroradiol 30(5):953–961. https://doi.org/10.3174/ajnr.A1470
19. Kleemann D, Nofz S, Schlottmann A, Höcker I, Stengel B (2007) Sinonasal sarcoidosis. HNO 55(12):956–960. https://doi.org/10.1007/s00106-006-1489-1
20. Al-Kofahi K, Korsten P, Ascoli C et al (2016) Management of extrapulmonary sarcoidosis: challenges and solutions. Ther Clin Risk Manag 12:1623–1634. https://doi.org/10.2147/TCRM.S74476
21. Aleksonienė R, Zeleckienė I, Matačiūnas M et al (2017) Relationship between radiologic patterns, pulmonary function values and bronchoalveolar lavage fluid cells in newly diagnosed sarcoidosis. J Thorac Dis 9(1):88–95. https://doi.org/10.21037/jtd.2017.01.17
22. Costabel U (1997) CD4/CD8 ratios in bronchoalveolar lavage fluid: of value for diagnosing sarcoidosis? Eur Respir J 10(12):2699–2700. http://www.ncbi.nlm.nih.gov/pubmed/9493645. Accessed 10 May 2017
23. Prasse A (2016) The diagnosis, differential diagnosis, and treatment of sarcoidosis. Dtsch Arztebl Int 113(33–34):565–574. https://doi.org/10.3238/arztebl.2016.0565
24. Baughman RP, Lower EE (2011) Who dies from sarcoidosis and why? Am J Respir Crit Care Med 183(11):1446–1447. https://doi.org/10.1164/rccm.201103-0409ED
25. Aloulah M, Manes RP, Ng YH et al (2013) Sinonasal manifestations of sarcoidosis: a single institution experience with 38 cases. Int Forum Allergy Rhinol 3(7):567–572. https://doi.org/10.1002/alr.21142
26. Pizarro C, Skowasch D, Grohé C (2017) Current therapeutic approaches to sarcoidosis. Dtsch Med Wochenschr 142(1):17–23. https://doi.org/10.1055/s-0042-109195
27. Baughman RP, Drent M, Kavuru M et al (2006) Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 174(7):795–802. https://doi.org/10.1164/rccm.200603-402OC
28. Reich JM (2002) Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. Chest 121(1):32–39. http://www.ncbi.nlm.nih.gov/pubmed/11796429. Accessed 11 May 2017
29. Hunninghake GW, Costabel U, Ando M et al (1999) ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffus lung Dis 16(2):149–173. http://www.ncbi.nlm.nih.gov/pubmed/10560120. Accessed 3 May 2017
30. Baughman RP, Winget DB, Bowen EH, Lower EE (1997) Predicting respiratory failure in sarcoidosis patients. Sarcoidosis Vasc Diffus lung Dis 14(2):154–158. http://www.ncbi.nlm.nih.gov/pubmed/9306506. Accessed 11 May 2017
31. McCaffrey TV, McDonald TJ (1983) Sarcoidosis of the nose and paranasal sinuses. Laryngoscope 93(10):1281–1284. http://www.ncbi.nlm.nih.gov/pubmed/6621225. Accessed 11 May 2017
32. Tay HL, Vaughan-Jones R, Qureshi SS (1994) Ethmoidal sarcoidosis. J Laryngol Otol 108(8):682–684. http://www.ncbi.nlm.nih.gov/pubmed/7930921. Accessed 11 May 2017
33. Nwawka OK, Nadgir R, Fujita A, Sakai O (2014) Granulomatous disease in the head and neck: developing a differential diagnosis. RadioGraphics 34(5):1240–1256. https://doi.org/10.1148/rg.345130068
34. Kirsten D (1995) Sarcoidosis in Germany. Analysis of a questionnaire survey in 1992 of patients of the German Sarcoidosis Group. Pneumologie 49(6):378–382. http://www.ncbi.nlm.nih.gov/pubmed/7644459. Accessed 27 April 2018
35. Mrówka-Kata K, Kata D, Lange D, Namysłowski G, Czecior E, Banert K (2010) Sarcoidosis and its otolaryngological implications. Eur Arch Oto-Rhino Laryngology 267(10):1507–1514. https://doi.org/10.1007/s00405-010-1331-y
36. van den Boer C, Brutel G, de Vries N (2010) Is routine histopathological examination of FESS material useful? Eur Arch Otorhinolaryngol 267(3):381–384. https://doi.org/10.1007/s00405-009-1097-2