Int J Clin Exp Pathol 2015;8(7):8438-8445
www.ijcep.com /ISSN:1936-2625/IJCEP0010559

Original Article

Rhinoscleroma: a detailed histopathological diagnostic insight

Ahmed RH Ahmed[1], Zeinab H El-badawy[1], Ibrahim R Mohamed[2], Waleed AM Abdelhameed[2]

Departments of [1]Pathology, [2]Ear Nose and Throat, Faculty of Medicine, Sohag University, Sohag, Egypt

Received May 22, 2015; Accepted June 28, 2015; Epub July 1, 2015; Published July 15, 2015

Abstract: Rhinoscleroma (RS) is a chronic specific disease of nose and upper respiratory passages caused by Klebsiella rhinoscleromatis bacilli. It is endemic in Egypt and in sporadic areas worldwide. Diagnosis of RS depends on identification of the pathognomonic Mickulicz cells (MCs) which is most prominent during granulomatous phase but spares or absent during catarrhal or sclerotic phases of the disease. This study aimed to identify the potential diagnostic features of nasal RS when MCs are absent. Nasal biopsies from 125 patients complaining of chronic nasal symptoms were retrieved for this study; including 72 chronic non specific inflammatory lesions and 53 RS diagnosed by PAS and Geimsa stains. The detailed histological differences among the two groups were measured statistically. RS was frequently a bilateral disease ($P < 0.05$) of young age ($P < 0.001$) with a female predominance ($P < 0.05$) and usually associated with nasal crustations ($P < 0.001$). Five strong histological indicators of RS were specified by univariate binary logistic regression analyses including squamous metaplasia (OR 27.2, $P < 0.0001$), dominance of plasma cells (OR 12.75, $P < 0.0001$), Russell bodies (OR 8.83, $P < 0.0001$), neutrophiles (OR 3.7, $P < 0.001$) and absence of oesinophiles (OR 12.0, $P < 0.0001$). According to Multivariate analysis, the diagnostic features of RS in absence of MCs can be classified into major criteria including dominance of plasma cells infiltration and absence of oesinophiles and minor criteria including young age, female gender, bilateral nasal involvement, nasal crustation, squamous metaplasia, Russell bodies, and neutrophiles. The diagnostic model using the two major criteria confirmed or excluded RS in 84.3% of the investigated cases.

Keywords: Rhinoscleroma, early diagnosis, absent Mickulicz cells, major and minor diagnostic criteria

Introduction

Rhinoscleroma (RS) is a chronic specific granulomatous disease of the upper respiratory tract. It is an endemic disease in Egypt as well in sporadic areas worldwide including Central America, Chili, Central Africa, India, Indonesia and Middle East countries [1-4]. The bacilli Klebsiella rhinoscleromatis; first described by Von-Frisch in 1882 [5] is the causative organism of RS. The exact pathogenesis of the disease is unclear, but infection is usually associated with crowded conditions and poor hygiene [6, 7].

Clinically, RS is a slowly progressive disease with insidious onset and indolent course affecting primarily the nasal cavity in 95 to 100% of cases with or without involvement of the nasopharynx, nasal sinuses, pharynx, larynx, trachea and bronchi [1, 8]. Isolated laryngo-tracheal RS without nasal involvement has been rarely reported [9]. The disease usually presents in the second and third decades of life, with a female predominance. It passes through three sequential but overlapping clinico-pathological phases: catarrhal/rhinitic, granulomatous/florid and sclerotic/cicatricial. Patients presented at initial catarrhal phase have features of non-specific rhinitis that evolves to chronic foul purulent discharge, repeated epistaxis, nasal obstruction, crustation and granulation as granulomatous phase develops. The clinical features of nasal RS are most prominent during granulomatous phase that usually develops several months or even years after infection with frequent remissions and relapses. If not treated early, the disease progresses to the final sclerotic phase where permanent complications including nasal deformities, anosmia, oral anesthesia, dysphonia, dysphagia and stridor could happen [10-13].

The presenting features and imaging techniques provide a presumptive diagnosis of RS but histopathological examination remains the mainstay for final definitive diagnosis. Catarrhal stage shows a nonspecific sub-epithelial infiltrate of polymorphonuclear leukocytes with granulation tissue. The diagnostic histological changes of RS are only seen during granulomatous phase. These include dense infiltration by lymphocytes, plasma cells, Russell bodies and the pathognomonic large Mikulicz cells; foamy macrophages with numerous cytoplasmic vacuoles containing viable and nonviable Klebsiella bacilli. Mickulicz cells are sparse or absent in the initial catarrhal and final sclerotic stages and most abundant during the second proliferative phase. Extensive fibrosis and less inflammatory cell infiltration are the main histological findings in the fibrotic phase [10, 11, 14, 15]. If numerous, the organism can be visualized within Mickulicz cells by H&E staining, however, intra-cytoplasmic bacilli are best demonstrated by special staining using periodic acid-Schiff (PAS), Geimsa, Gram, silver or Warthin-Starry stains. More specifically, type III Klebsiella antigen can be detected by immunohistochemistry and the tissue culture can demonstrate the organism in about 50% of cases in particular at the granulomatous stage of the disease [14-16].

Early diagnosis and treatment of RS are necessary to avoid progressive and destructive complications of the disease. Apart from culture studies, other diagnostic techniques are based predominantly on detection of Miculicz cells. Hence, histological confirmation of RS is challenging when Mickulicz cells are deficient. In addition, foamy histeocytes that simulate Mickulicz cells are readily seen in other granulomatous lesions of the upper airodigestive regions including leprosy, tuberculosis, Wegener's granulomatosis and sarcoidosis [6, 14, 17]. This study was designated to investigate the detailed pathological changes of RS in order to identify the potential early histopathological diagnostic features of the disease when Mickulicz cells are absent.

Materials and methods

This is a retrospective study conducted within Departments of Pathology at Sohag University Hospital, Upper Egypt. Approval to perform this work was obtained from the institutional Research Ethical Committee. Data of clinical history and examination were obtained from patients' clinical files. All patients underwent nasal punch biopsies at Ear, Nose and Throat (ENT) department for diagnostic purposes of chronic nasal symptoms between January 2011 and December 2013 using endoscopic examination with 0° and 30° telescopes. The inclusion criteria were clinical suspicious of rhinoscleroma and unexplained long standing nasal manifestations including nasal obstruction, nasal crustation or repeated epistaxis. Presence of benign or malignant neoplastic lesions was the main exclusion criterion.

Formalin-fixed paraffin-embedded tissue blocks of nasal biopsies of 125 patients were included in this study. Sections of 5 μm thickness were stained with PAS (DDK Italia, code 14-122) and Geimsa stains (DDK Italia, code 14-120) for identification of Klebsiella rhinoscleromatis organism and for acid fast bacteria stain (Biostain ready reagent Ltd, KT 021) to exclude possibility of mycobacterium infection. All staining steps were performed at room temperature. Briefly, the tissue sections were deparafinized in xylene, rehydrated in down-graded alcohol and rinsed in distilled water for two minutes. For PAS stain, the sections were incubated in periodic acid for 10 minutes, washed in distilled water, incubated in Schiff reagent for 15 minutes followed by differentiation in two changes of sodium metabisulphide. The sections were then washed twice in distilled water and counterstained by Mayer hematoxylin. For Geimsa stain, the sections were incubated in working Geimsa solution for 20 minutes, washed in distilled water before differentiation in 0.5% acetic acid. For acid fast bacilli stain, the sections were incubated in carbol fuchsin solution for 15 minutes, rinsed thoroughly in tap water, differentiated for seconds in 1% acid alcohol and washed in running tap water for 1 minute before staining by methylene blue for 1 minute. All sections were then dehydrated in up-graded alcohol, cleared in xylene and mounted as usual.

The H&E stained sections and sections stained with special stains were evaluated by two pathologists independently without prior knowledge of the clinical data. The detailed histopathological findings including status of covering epithelium, intensity of inflammatory reaction, type and relative dominance of inflamma-

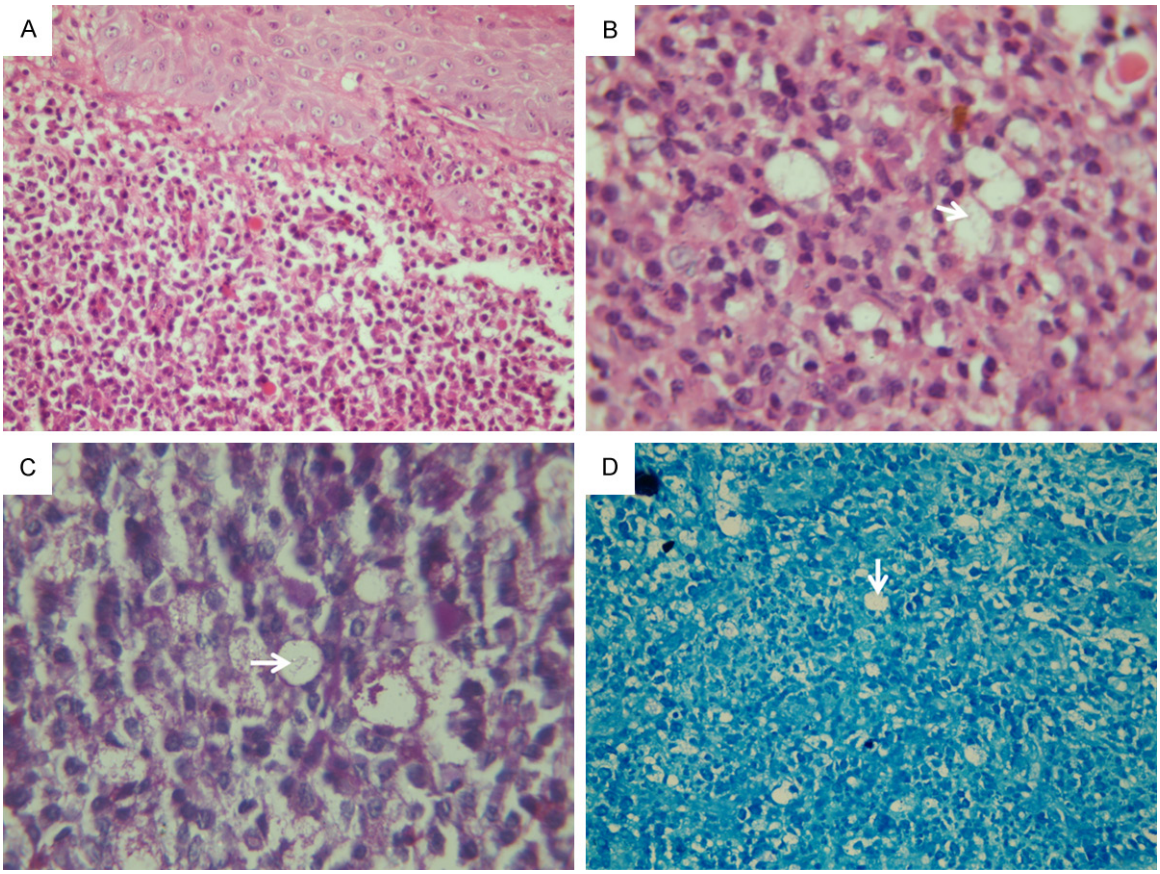

Figure 1. Dominance of plasma cells and squamous metaplasia (A), dominance of plasma cells and absence of esinophiles (B) and demonstration of Klebsiella Rhinoscleromatis bacilli within Mickulicz cells by H&E (B), PAS (C) and Geimsa (D) stains (arrows). Magnification is × 400 (A and D) and × 1000 (B and C).

tory cells and presence of fibrosis were evaluated. For identification of Klebsiella organism; PAS-stained red or purple cytoplasmic rods or Geimsa-stained blue cytoplasmic rods were considered positive.

The commercially available statistical software (IBM-SPSS version 19.0 for Windows; IBM Inc) was used for data analysis. The frequency of a categorical observation among non specific inflammatory and rhinoscleroma groups was compared by Chi-Square Test (χ^2). Association among different groups was tested by Spearmann's rho correlation co-efficient and Mann-Whitney *U* Test was used to compare continuous variables among different study groups. To adjust the potential diagnostic variables of rhinoscleroma and to single out independent diagnostic factor(s), univariate and multivariate binary logistic regression analysis were undertaken by stepwise selection. The cut-off for significance of all used statistical analyses was rated as $P < 0.05$.

Results

A total of 125 tissue biopsies were retrieved for this study including 79 females and 46 males. The patients' age ranged between 12 and 72 years with a mean (SD) value of 37.07 (16.9) years and a median value of 35 years. Most of the patient's (89.6%) had combined nasal complaints; the most frequent of which was nasal obstruction that had been reported in 104 patients. Nasal discharge, nasal granulation/crustation, repeated epistaxis and nasal polypi were reported in 80, 62, 21 and 28 patients, respectively. Most of the patients (n = 71) had bilateral nasal manifestations while unilateral right or left side nasal symptoms were reported in 30 and 24 patients, respectively.

The provisional clinical assessment suspected RS in 68 patients and the remaining were reported as chronic non specific inflammation. Based on detection of Mickulicz cells in the

Table 1. The clinical and histopathological features of the investigated cases

Variable	All cases	Rhinoscleroma (n = 53)	Other inflammatory lesions (n = 72)	*P* value
Clinical features				
Age (years)				
Minimum	12	12	14	
Maximum	72	60	72	0.01**
Mean (SD)	37.1 (16.9)	31.3 (14.2)	42.3 (17.6)	
Median	35	25	40	
Sex				
Female	79	30	40	0.039*
Male	46	32	14	
Affected side				
Unilateral	54	17	37	0.031*
Bilateral	71	36	35	
Nasal obstruction				
Yes	104	44	60	0.96*
No	21	9	12	
Nasal discharge				
Yes	80	34	46	0.98*
No	45	19	26	
Epistaxis				
Yes	21	10	11	0.59*
No	104	43	61	
Nasal crustation				
Yes	62	38	24	0.0001*
No	63	15	48	
Nasal polyp				
Yes	28	0	28	0.0001*
No	97	53	44	
Histological findings				
Covering epithelium				
Columnar	39	2	37	
Squamous	79	47	32	0.0001*
Shedded	7	4	3	
Inflammatory reaction				
Dense	78	37	41	
Moderate	47	16	31	0.142*
Lymphocytes				
Yes	125	53	72	
No	0	0	0	NA
Plasma cells				
Yes	125	53	72	
No	0	0	0	NA
Russel bodies				
Yes	48	35	13	
No	77	18	59	0.0001*
Esinophiles				
Yes	57	8	49	
No	68	45	23	0.0001*

Neutrophiles				
Yes	60	35	25	
No	65	18	47	0.001*
Dominant inflammatory cell				
Lymphocytes	38	4	34	
Plasma cells	65	39	26	
Mickulicz cells	10	10	0	0.0001*
Esinophiles	12	0	12	
Fibrosis				
Yes	49	20	29	
No	76	33	43	0.774*

* Chi Square test, ** Spearmann's rho correlation co-efficient test.

Table 2. Diagnostic indicators of RS based on univariate regression analysis

Variable	95% CI		Odds ratio	*P* value
	Upper	Lower		
Female versus male patient	4.80	1.03	2.23	0.041
Age ≤ 25 versus Age > 25 years	6.14	1.37	2.90	0.006
Bilateral versus unilateral nasal symptoms	4.69	1.07	2.24	0.033
Presence of nasal crustation	10.97	2.34	5.07	0.0001
Presence of squamous metaplasia	120.82	6.11	27.17	0.0001
Plasma cell-dominant versus lymphocyte-dominant inflammatory reaction	40.21	4.04	12.75	0.0001
Presence of russell bodies	20.18	3.86	8.83	0.0001
Presence of neutrophiles	7.71	1.73	3.66	0.001
Absence of oesinophiles	29.49	4.87	11.98	0.0001

standard H&E stained sections, the patients had been classified into three categories; patients diagnosed as RS (n = 38), patients diagnosed as chronic non specific inflammatory lesions (n = 60) and patients suspected for RS (n = 27) and required special staining for confirmation. The final diagnosis of all patients was established after special staining using PAS, Geimsa and MZN stains. RS bacilli were demonstrated by PAS and Geimsa in 53 cases and absent in the remaining cases which were considered as chronic non specific inflammatory lesions (**Figure 1**). None of the tissue samples showed positive intracellular organism for MZN stain.

Different clinical parameters and histological findings of RS and chronic non specific inflammatory lesions have been compared (**Table 1**). RS is a disease of young age (Mann-Whitney U, $P = 0.001$) with a significantly lower mean and median age for RS patients compared to patients with other chronic inflammatory lesions (Spearmann's rho correlation coefficient = 0.288, $P = 0.01$). Additionally, RS tends to be more incident among females than males [χ^2 (2) = 4.27, $P = 0.039$] and more frequently a bilateral nasal disease [χ^2 (2) = 4.64, $P = 0.031$]. Although both RS and other inflammatory lesions were presented with combined clinical features, nasal crustation was significantly more incident in RS patients [χ^2 (2) = 17.97, $P = 0.001$] while nasal polyps were significantly more frequent in inflammatory lesions other than RS [χ^2 (2) = 26.56, $P = 0.001$].

On histological evaluation, strong and moderate inflammatory reactions were reported in 78 and 47 cases, respectively and superimposed acute inflammatory reaction was recorded in 60 cases of which one showed dense infiltration by neutrophiles. Although all biopsies showed infiltration by plasma cells and lymphocytes, the dominant inflammatory cells were plasma cells in 65 lesions, lymphocytes in 38 lesions, Mikulicz' cells in 10 lesions and oesinophiles in 12 lesions. Both plasma cells and lymphocytes were distributed evenly through the lesions. The covering epithelium was columnar (n = 39), with squamous metaplasia (n =

79) or completely shedded in 7 cases. None of the evaluated biopsies showed epithelial dysplasia. Mild background fibrosis was detected in 49 cases. Mikclicz' cells were identified by H&E stain in 37 cases and suspected in 28 cases of which 16 were confirmed by PAS and Geimsa stains. Statistically, plasma cells predominated more frequently in biopsies of RS and lymphocytes predominated in other inflammatory lesions [χ^2 (2) = 24.14, P = 0.001]. Other cellular components that are strongly associated with rhinoscleroma were presence of Russell bodies [χ^2 (2) = 29.71, P = 0.001] and neutrophiles [χ^2 (2) = 11.99, P = 0.01]. On the other extreme, oesinophiles are usually absent or scarce in cases of rhinoscleroma and their presence suggests other inflammatory lesions [χ^2 (2) = 34.52, P = 0.001].

The diagnostic accuracy of different clinical and histological features other than presence of MCs was measured using Binary Logistic regression analysis. According to univariate regression analyses (**Table 2**), female patients aged less than 25 years presented with bilateral nasal symptoms including nasal crustation and histologically showed squamous metaplasia, dominant plasma cell infiltrate in addition to Russell bodies and neutrophiles with absence of oesinophiles have almost RS infection.

The relative importance of these nine variables; age, sex, bilateralism, nasal crustation, dominance of plasma cells as well as presence of squamous metaplasia, Russell bodies, neutrophiles and absence of esinophiles to diagnose RS regardless presence of MCs was tested by forward stepwise multivariate binary logistic regression analysis. Of these parameters, dominance of plasma cells followed by absence of oesinophiles is the strongest diagnostic indicators of RS infection. The diagnostic model using these two variables was able to accurately confirm or exclude RS in 84.3% of the investigated cases. This percentage rose to 87% when the nine parameters were included in the diagnostic model.

Based on these models diagnostic features of RS in absence of MCs can be classified into major criteria including dominance of plasma cells infiltration and absence of esinophiles and minor criteria that include young age, female gender, bilateral nasal involvement, presence of squamous metaplasia, presence of nasal crustation, presence of Russell bodies, and presence of neutrophiles.

Discussion

Rhinoscleroma is a chronic indolent infection of the nose and upper respiratory passages. It has been frequently described as a rare disease; therefore, national and international epidemiological data are scarce [1, 18]. In this study, 53 cases of RS were diagnosed during three years period in only one medical center across south of Egypt; which could argue against rarity of this disease at least in Egypt. Gaffar *et al* [8] reported 56 new cases of RS in one main medical center at north of Egypt along 10 years period which is likely less than the number recorded in this study and implies that RS is more incident in Upper Egypt. The reported rarity of RS could be explained by its diagnosis only after full development of the characteristic clinical and pathological features. Cases at the pre-diagnostic stage that usually extends for months or years [1, 13, 18] and could involve larger number of individuals are not always considered among RS patients. This study was designated to find out reliable histological diagnostic criteria of RS regardless detection of MCs-rich inflammatory reaction of the disease.

The general clinical features of our investigated RS patients; being more common in young age, more incident among females and presents predominantly by bilateral nasal discharge and nasal crustation are concordant to previously reported studies [8, 11, 14]. Moreover, the histological findings reported in this study are consistent with the previously agreed criteria for diagnosis of RS [10, 14, 15, 19, 20]. Identification of MCs is the pathognomonic histological criterion for diagnosis of RS. However, detection of MCs in H&E stained sections is sometimes challenging particularly in the early catarrhal or late fibrotic stage of the disease [10, 13, 14]. Thirty eight of RS patients in this study were at florid stage of the disease while no MCs could be detected by H&E staining in the remaining 15 cases that represent a considerable fraction of RS patient's with suspicious clinical features. On the other hand 12 patients of non specific inflammatory nasal lesions were suspected for RS with H&E staining. This finding ensures that long standing

chronic non specific inflammatory lesions of the nose, which is far more common than RS could be confusing histologically with RS when MCs are absent. Overall, it was difficult to identify/exclude MCs by the basic H&E staining in 27 (21.6%) of the investigated cases and special staining of the bacilli was required for confirmation. Several clinical and histological findings could favor diagnosis of RS over other chronic non specific inflammatory lesions (**Table 1**). According to univariate and multivariate analyses, the diagnostic features of RS in absence of MCs can be classified into major criteria including dominance of plasma cells infiltration and absence of esinophiles and minor criteria that include young age, female gender, bilateral nasal involvement, presence of nasal crustation, presence of squamous metaplasia, presence of Russell bodies and presence of neutrophiles. The diagnostic model using the two major criteria confirmed or excluded RS accurately in 84.3% of the cases. Abalkhail A et al [15] reported that plasma cells are more prominent than lymphocytes in biopsies of 29 investigated cases of RS. In his 55 investigated patients, Pattankar et al [19] reported that lymphocytes and plasma cells were seen consistently along with MCs in all RS cases while oeosinophils were occasionally seen in only three cases. Even during the granulomatous phase of RS, the demonstrated MCs are usually much less numerous in places of heavy plasma cell infiltration [21]. In addition, Russel bodies which are frequent histological findings in RS are originally modified plasma cell [22]. All these provided data support our proposed importance of plasma cells as a reliable diagnostic finding of RS. The exact reason for dominance of plasma cells compared to lymphocytes in cases of RS is unclear. Berron et al [23] showed that cellular immune response is defective in cases of RS with reduced CD4/CD8 ratio and diminished T cell response. The histeocytes fail to transform to epithelioid cells that have powerful phagocytic and defensive effect against the organism. In the same context, it has been showed that humoral immunity which is based mainly on functioning plasma cells is the main response against RS infection; which could explain plenty of plasma cells in RS inflammatory reaction [24, 25].

Rhinoscleroma is a diagnostic and therapeutic challenge due to its chronic course, need for prolonged treatment and repeated relapses [1, 14]. In his case series, Tan *et al* [26] concluded that early detection is essential for proper treatment of this disease. The duration of exposure to the organism during which living in an endemic area or in close contact with an affected patient is very long and the period between occurrence of symptoms and diagnosis of the disease may extend from months to years [18]. Our proposed diagnostic scheme can be applied for early detection of RS before development of full-blown histological features of the disease. Furthermore, it can be used for screening of high risk individuals in endemic areas from whom culture studies are mostly negative. Early diagnosis of such cases would reduce duration of treatment, reduce rates or prevents relapse and prevent progression and complications of the disease. This diagnostic scheme can be also applied for early detection and treatment of the relapsed cases which could even help eradication of the disease.

To conclude, RS is not a rare disease among Egyptians. Dominance of plasma cells and absence of oesinophiles in biopsies from patients with chronic nasal symptoms should raise the possibility of RS regardless detection of MCs particularly in endemic areas.

Acknowledgements

This work was partly sponsored by academic research grants, Faculty of Medicine, Sohag University, Egypt. Thanks to Marwa Mohammed and Walaa Abdelmohsen, the laboratory specialists, Pathology Department, Faculty of Medicine, Sohag University for their kind advice and support for preparation of histological sections and special staining.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ahmed Roshdi Hamed Ahmed, Department of Pathology, Faculty of Medicine, Sohag University, Sohag P082524, Egypt. Tel: 002 01069329600; Fax: +20 0934602963; E-mail: ahmed_ahmed4@med.sohag.edu.eg; aa_roshdi@yahoo.com

References

[1] Hart CA, Rao SK. Rhinoscleroma. J Med Microbiol 2000; 49: 395-6.

[2] Muzyka MM, Gubina KM. Problems of the epidemiology of scleroma. I. Geographical distribution of scleroma. J Hyg Epidemiol Microbiol Immunol 1971; 15: 233-42.
[3] Muzyka MM, Gubina KM. Problems of the epidemiology of scleroma. 2. Some aspects of the problem of endemic focus formation. J Hyg Epidemiol Microbiol Immunol 1972; 16: 8-20.
[4] Chan TV, Spiegel JH. Klebsiella rhinoscleromatis of the membranous nasal septum. J Laryngol Otol 2007; 121: 998-1002.
[5] Von-Frisch A. Zur. Aetiologie des Rhinscleroms. Wien Med Wochenschr 1882; 32: 96-7.
[6] Montone KT. Infectious diseases of the head and neck: a review. Am J Clin Pathol 2007; 128: 35-67.
[7] Fernandez-Vozmediano JM, Armario Hita JC, Gonzalez Cabrerizo A. Rhinoscleroma in three siblings. Pediatr Dermatol 2004; 21: 134-8.
[8] Hazem A. Gaafar, Alaa H. Gaafar, Yasser A. Nour. Rhinoscleroma: An updated experience through the last 10 years. Acta Oto-Laryngologica 2011; 131: 440-6.
[9] Iyengar P, Laughlin S, Keshavjee S, Chamberlain DW. Rhinoscleroma of the larynx. Histopathology 2005; 47: 224-5.
[10] Zhong Q, Guo W, Chen X, Ni X, Fang J, Huang Z, Zhang S. Rhinoscleroma: a retrospective study of pathologic and clinical features. J Otolaryngol Head Neck Surg 2011; 40: 167-74.
[11] Fawaz S, Tiba M, Salman M, Othman H. Clinical, radiological and pathological study of 88 cases of typical and complicated scleroma. Clin Respir J 2011; 5: 112-21.
[12] Bailhache A, Dehesdin D, Francois A, Marie JP, Choussy O. Rhinoscleroma of the sinuses. Rhinology 2008; 46: 338-41.
[13] Thompson LD. Rhinoscleroma. Ear Nose Throat J 2002; 81: 506.
[14] Panna Mahadevia, Margaret Brandwein-Gensler. Infectious Diseases of the Head and Neck. Surgical Pathology of the Head and Neck. Edited by BARNES L, 3 edition. New York: Informa Healthcare; 2009. pp. 1609-716.
[15] Abalkhail A, Satti MB, Uthman MA, Al Hilli F, Darwish A, Satir A. Rhinoscleroma: a clinicopathological study from the Gulf region. Singapore Med J 2007; 48: 148-51.
[16] Meyer PR, Shum TK, Becker TS, Taylor CR. Scleroma (Rhinoscleroma). A histologic immunohistochemical study with bacteriologic correlates. Arch Pathol Lab Med 1983; 107: 377-83.
[17] Zafar U, Khan N, Afroz N, Hasan SA. Clinicopathological study of non-neoplastic lesions of nasal cavity and paranasal sinuses. Indian J Pathol Microbiol 2008; 51: 26-9.
[18] de Pontual L, Ovetchkine P, Rodriguez D, Grant A, Puel A, Bustamante J, Plancoulaine S, Yona L, Lienhart PY, Dehesdin D, Huerre M, Tournebize R, Sansonetti P, Abel L, Casanova JL. Rhinoscleroma: a French national retrospective study of epidemiological and clinical features. Clin Infect Dis 2008; 47: 1396-402.
[19] Pattankar VL, Roohi S, Reddy BN. Clinicopathological study of Rhinoscleroma with Mast cell profile. International Journal of Scientific and Research Publications 2013; 3: 1-5.
[20] Sood N, Sood S, Arora S. Cytohistological features of rhinoscleroma. Indian J Pathol Microbiol 2011; 54: 806-8.
[21] Hoffmann EO, Loose LD, Harkin JC. The Mikulicz cell in rhinoscleroma. Light, fluorescent and electron microscopic studies. Am J Pathol 1973; 73: 47-58.
[22] Toppozada H, Riad W, Michaels L, Gaafar H, Sid-Ahmed K. The epithelium and chronic inflammatory cells in scleroma. (An electron microscopic study). J Laryngol Otol 1981; 95: 1049-57.
[23] Berron P, Berron R, Ortiz-Ortiz L. Alterations in the T-lymphocyte subpopulation in patients with rhinoscleroma. J Clin Microbiol 1988; 26: 1031-3.
[24] Dogheim Y, Maher A, el-Sawy M. Serum immunoglobulin levels in rhinoscleroma contacts. J Laryngol Otol 1986; 100: 171-3.
[25] Modlin RL, Hofman FM, Meyer PR, Sharma OP, Taylor CR, Rea TH. In situ demonstration of T lymphocyte subsets in granulomatous inflammation: leprosy, rhinoscleroma and sarcoidosis. Clin Exp Immunol 1983; 51: 430-8.
[26] Tan SL, Neoh CY, Tan HH. Rhinoscleroma: a case series. Singapore Med J 2012; 53: 24-7.