Rheumatic disorders affecting the head and neck: underestimated diseases

Andreas Knopf¹, Murat Bas¹, Adam Chaker¹, Ulrich Strassen¹, Anja Pickhard¹, Thomas Stark¹, Tobias Lahmer² and Klaus Thürmel²

Abstract

Objectives. To describe the clinical manifestations of rheumatic disorders with isolated head and neck (H&N) affection and to introduce a novel diagnostic pathway.

Methods. From 2004 to 2010, 90 patients presented with isolated H&N symptoms of a rheumatic disorder were included in the study. Rheumatic disorders were classified according to the ACR criteria. In 2008, we introduced a novel diagnostic pathway to reduce under-diagnosis of primary rheumatic disorders in the H&N. Disease-related data were assessed retrospectively and set into clinical context.

Results. The majority of patients suffered from SS (n=42), granulomatosis with polyangiitis (Wegener’s) (n=13) and sarcoidosis (n=18) with predominance for female patients (n=65). Enlargement of the major salivary glands (n=47), sicca symptoms (n=41) and cervical lymphadenopathy (n=25) represented the most frequent symptoms. Interestingly, 3% of all enlargements of salivary glands and 4% of all cervical lymphadenopathy could be contributed to rheumatic disorders. The mean time to diagnosis was 20.71 months for SS, 8.4 months for granulomatosis with polyangiitis and 57.5 months for sarcoidosis. After implementation of the newly developed diagnostic pathway in 2008, the annually diagnosed rheumatic disorders increased 5-fold.

Conclusions. The majority of rheumatic diseases of the H&N can be related to SS, granulomatosis with polyangiitis and sarcoidosis. However, the lack of specific symptoms and the clinical variability of H&N manifestation may contribute to a prolonged time to diagnosis. Our retrospective study points out the variability of symptoms and suggests a diagnostic pathway to reduce the cases of undetected H&N affection in rheumatic disorders.

Key words: Rheumatic disorder, Head and neck, Sarcoïdosis, Granulomatosis with polyangiitis (Wegener’s), Sjögren’s syndrome.

Introduction

Rheumatic disorders are considered as systemic disease. Isolated local disease expression of rheumatic conditions in the head and neck (H&N) is considered as an uncommon event. However, some important rheumatic diseases particularly concern H&N practitioners. For instance, SS typically affects the H&N region [1, 2]. In granulomatosis with polyangiitis (Wegener’s), upper airway and sinonasal manifestation are common precursors to systemic impairment [3]. Other entities, such as sarcoidosis, are attributed to pulmonary manifestation and can appear with an exclusive H&N affection [4, 5]. The lack of specificity and the variability of H&N symptoms of rheumatic disorders require precise diagnostic effort [1, 6, 7]. Numerous differential diagnoses referring to inflammatory or neoplastic diseases have to be considered in the diagnostic management. Therefore, the estimated number of non- or misdiagnosed cases might be immense. In this current study, we demonstrate symptoms of patients with isolated rheumatic disorders of the H&N region in our cohort. We recommend a simple but effective diagnostic pathway.
Patients and methods

From January 2004 to July 2010, more than 40,000 patients were treated in the outpatient clinic of the Department of Otolaryngology and Head and Neck Surgery, Technical University Munich. Rheumatic disorders of the H&N were diagnosed in more than 120 patients representing around 3 per 1000 of the overall patient population. In this retrospective study, medical records were subjected to standardized assessment of available disease-related data: mean age at diagnosis, mean time to diagnosis, distribution between sexes, symptoms and cases per year. A total of 90 patients with isolated H&N symptoms at the time of diagnosis were included in this study. Rheumatic disorders were classified according to the ACR criteria. Since 2008, patients who did not suffer from infectious or neoplastic diseases underwent a novel diagnostic pathway to evaluate the amount of undiagnosed rheumatic diseases. This pathway was applied to patients with clinical discrepancy between low symptom burden and relevant clinical manifestation. Acute, recurrent or persistent disease occurred. To evaluate systemic involvement of suspected rheumatic conditions, we assessed differential blood count, CRP, ESR, sodium, potassium, calcium, kidney and liver parameter. Patients who were subsequently attributed to infectious diseases with subclinical courses underwent first-line calculated antibiotic therapy. Patients with symptoms refractory to antibiotic treatment or per se inconspicuous blood results were tested for further inflammatory markers (ferritin, C3/4 complement factors and serum electrophoresis), ANCA, angiotensin-converting enzyme (ACE), ANA, ENAs and rheuma factor (RF).

In addition, histological examinations were conducted in patients with persistent pathologies visualized in H&N US imaging. Further examinations, e.g. chest X-ray/CT scan, abdominal US and urine sediment testing were performed in patients with elevated autoantibodies to exclude a possible systemic impairment (Fig. 1).

Results

Epidemiology of rheumatic disorders affecting the H&N

A total of 90 patients presented with primary H&N symptoms were included in our study. Forty-seven (52%) patients suffered from collagenosis, 19 (21%) patients from vasculitis, 18 (20%) patients from sarcoidosis and 6 patients from rare or undifferentiated diseases. The mean age at the time of diagnosis was 52.1 years and the mean time to diagnosis was 25.1 months. We determined a female predominance of 2.6:1. Of 90 patients, 73 (81%) could be contributed either to SS (47%), granulomatosis...
with polyangiitis (14%) or sarcoidosis (20%). With respect
to this most frequent diseases group, the mean age at
diagnosis ranged from 39.4 (sarcoidosis) to 56.2 (SS)
years. Mean time to diagnosis was 8.4 months for granu-
lomatosis with polyangiitis, whereas time to diagnosis is
notably prolonged for SS (20.7 months) or sarcoidosis
(57.5 months). We detected a moderate female predom-
inance for granulomatosis with polyangiitis (2.3 : 1). In con-
trast, SS showed an impressive gender bias resulting in
a female predominance of 8.4 : 1. There was no gender
predominance for sarcoidosis (Table 1).

Symptoms of rheumatic disorders affecting the H&N

In our cohort, we could recognize a symptom pattern
including 11 symptoms only. Enlargement of major saliv-
ary glands, sicca symptoms as well as cervical lymph-
adenopathy were the most frequent symptoms and
appeared in both SS and sarcoidosis, respectively.
Recurrent facial swelling, facial or cranial pain, rhinorrhoea
and facial palsy occurred infrequently. Patients with

Table 1 Distribution of rheumatic disorders affecting
the H&N

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean (±S.D.) age at diagnosis, years</th>
<th>Mean (±S.D.) time to diagnosis, months</th>
<th>Female:male ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 90)</td>
<td>52.1 (16.9)/25.1 (77.2)</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Collagenosis (n = 47)</td>
<td>56.8 (17.2)/20.4 (34.8)</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>SS (n = 42)</td>
<td>56.2 (15.0)/20.7 (36.3)</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Scleroderma (n = 1)</td>
<td>-/-</td>
<td>-/-</td>
<td></td>
</tr>
<tr>
<td>MCTD (n = 4)</td>
<td>63.5 (16.8)/17.3 (17.6)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vasculitis (n = 19)</td>
<td>52.9 (16.2)/5.9 (9.3)</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>WD (n = 13)</td>
<td>48.9 (17.3)/8.4 (10.4)</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis (n = 6)</td>
<td>61.5 (10.1)/3.9 (0.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis (n = 18)</td>
<td>39.4 (16.6)/57.5 (155.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rare and undifferentiated</td>
<td>51.2 (18.7)/20.0 (15.6)</td>
<td>1</td>
<td></td>
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</tbody>
</table>

WD: granulomatosis with polyangiitis.

Table 2 Primary H&N symptoms at the time of diagnosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All (n = 90)</th>
<th>SS (n = 42)</th>
<th>WD (n = 13)</th>
<th>Sarc. (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlargement of salivary glands, n (%)</td>
<td>47 (54.0)</td>
<td>33 (79.0)</td>
<td>0</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Sicca symptoms, n (%)</td>
<td>43 (47.8)</td>
<td>42 (100)</td>
<td>0</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Lymphadenopathy, n (%)</td>
<td>25 (28.7)</td>
<td>10 (25.6)</td>
<td>0</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Facial/cranial pain, n (%)</td>
<td>9 (10.3)</td>
<td>0</td>
<td>3 (23.1)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Rhinorrhoea, n (%)</td>
<td>8 (9.2)</td>
<td>0</td>
<td>6 (46.2)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Facial swelling, n (%)</td>
<td>5 (5.8)</td>
<td>2 (5.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Otorrhea, n (%)</td>
<td>5 (5.8)</td>
<td>0</td>
<td>4 (30.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea/dysphonia, n (%)</td>
<td>4 (4.6)</td>
<td>0</td>
<td>2 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent epistaxis, n (%)</td>
<td>2 (2.2)</td>
<td>0</td>
<td>2 (15.4)</td>
<td>0</td>
</tr>
<tr>
<td>Facial palsy, n (%)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Diplopia, n (%)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>1 (7.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

WD: granulomatosis with polyangiitis; Sarc.: sarcoidosis.
to establish a diagnostic pathway to reduce the count of undiagnosed cases (Fig. 1). With respect to the H&N region, a rheumatic disorder has to be considered when patients suffer from (per-) acute, recurrent or persistent disease with a striking clinical discrepancy between low symptom burden and distinct clinical findings. Differential blood count, CRP, ESR, sodium, potassium, calcium, kidney and liver parameters were assessed to get a rough and quick breakdown and to exclude a possible systemic involvement. Most patients can be considered to be cases with infectious diseases with subclinical courses. These patients showed a leucocytosis with atypical lymphocytes along with ESR/CRP elevation indicative of mononucleosis; raised white blood cell counts with reactive left-shift and ESR/CRP elevation suggested bacterial infection, respectively. These patients underwent calculated first-line antibiotic treatment or supportive therapy. Patients with pathological left-shift or immature blood precursors in the differential blood counts were referred to a haematologist. Patients with refractory antibiotic therapy or without signs of acute inflammatory disease were additionally screened for immunological markers. SS or sarcoidosis was considered when glandular and lymph node enlargement occurs (per-) acute with a striking discrepancy between profuse parenchymatous enlargement but minor dolorousness (dull capsule pain). These patients were additionally tested for ANA/ENA, ACE and RF; patients with sinonasal symptoms suggesting granulomatosis with polyangiitis were tested for ANCA (PR3, MPO). C3/C4, ferritin and electrophoresis were analysed to identify hidden inflammatory disease. All patients with persistent pathologies in the H&N US without positive blood test or surrogate parameters of sarcoidosis under- went intra-lesional biopsy. Lymph node extirpation was performed in patients screened for Sjögren’s with concomitant cervical lymphadenopathy to exclude mucosa-associated lymphoid tissue (MALT) lymphoma. Salivary gland biopsy was performed in patients with incomplete symptomatology o/a blood tests for SS. In addition, nasal mucosal biopsies were routinely performed in patients who were suspected for vasculitis. Abdominal US, chest X-ray (CT) and urine sediment were finally added in patients with a newly diagnosed rheumatic disorder of the H&N.

After introduction of this pathway in 2008, we routinely diagnosed 5-fold more patients with rheumatic disorders (mean of cases from January 2004 to December 2007: 4.25; mean of cases from January 2008 to July 2010: 24). From January 2004 to December 2007, we diagnosed nine patients (0.19 cases per month) with SS; in the time from January 2008 to July 2010, we detected 38 cases (1.3 cases per month). With respect to sarcoidosis or Wegener’s disease, the number of diagnosed cases increased 5-fold (2004–07: 2 cases; 2008–10: 11 cases) or by factor 5.5 (2004–07: 3 cases; 2008–10: 15 cases), respectively (Fig. 2).

Discussion

Most rheumatic disorders show a systemic impairment and represent a substantial part of internal medicine, but some rheumatic disorders predominantly affect the H&N region or show a phase-dependent involvement of H&N organs. Literature lacks comprehensive analysis of H&N manifestation. Therefore, published data from patients that exclusively suffer from H&N symptoms are underrepresented.

The current study demonstrates clinical data from a cohort including 90 patients with isolated H&N symptoms at the time of diagnosis. Eighty-one per cent of these can be classified as only three major diseases. Forty-two (47%) patients suffered from SS, 18 (20%) from sarcoidosis and 13 (14%) from granulomatosis with polyangiitis. Granulomatosis with polyangiitis is a rare disorder. Descriptive epidemiological studies suggested an estimated prevalence from 24 to 157 per million and annual incidence rate from 3 to 14 per million. Granulomatosis with polyangiitis (Wegener’s) affects middle-aged people with slight predominance for men [8, 9]. In our cohort, granulomatosis with polyangiitis exhibits a moderate gender bias resulting in a female predominance of 2:3:1. The initial involvement of the H&N, particularly the nose and paranasal sinuses or the middle ear is frequent and well known to the ENT surgeon. The clinical course in granulomatosis with polyangiitis commonly appears in the upper airways in early stages followed by systemic (renal or pulmonary) impairment [3, 10]. Concordant with the present literature, the majority of primary symptoms were closely associated with the sinonasal system [3]. Of 13 patients, 12 (92%) suffered from sinonasal symptoms, presenting with severe nasal crusting (46.2%), recurrent epistaxis (15.4%), facial/cranial pain (23.1%) due to chronic sinusitis and diplopia due to infiltrating sinonasal masses (7.6%). Otological symptoms occurred in four (30.8%) patients along with the sinonasal
manifestation. None of our patients exhibited saddle nose deformity at the time of diagnosis. The mean time to diagnosis in granulomatosis with polyangiitis was 8.4 months. The rather short delay to diagnosis can be explained by: (i) an implemented knowledge about Wegener’s H&N symptomatology; (ii) indicative clinical picture; and (iii) effortless gain of biopsies.

In contrast, the mean time to diagnosis in sarcoidosis is very prolonged and consumes ~58 months. Unspecific enlargement of cervical lymph nodes and major salivary glands remain the most frequent symptoms. Five (27.8%) patients suffered from sicca symptoms as well. Other H&N clinicians also report on xerostomia associated with sarcoidosis [11-14]. Rhinorrhea as a surrogate symptom of sinonasal involvement was observed once and identified the sinonasal system being an infrequent region of H&N manifestation [15-17]. Surprisingly, only one patient exhibited Heerfordt syndrome, which is classically attributed to the H&N. From November 1996 to June 1999, 10 medical centres (from across the USA) and one coordinating centre conducted a Case Control Etiologic Study of Sarcoidosis (ACCESS) including 736 patients. Six hundred and ninety-nine patients had a thoracic involvement, 368 had concomitant extrathoracic disease, but isolated extrathoracic sarcoidosis was observed in only 14 cases [4]. The prevalence of extrapulmonary sarcoidosis varies among populations from 0.3 to 50% [18]. In our study, we report on 18 isolated extrathoracic sarcoidosis from one department, suggesting that the H&N manifestation is rather underdiagnosed. The most striking explanation might be the lack of specific symptoms and the clinical variability of H&N manifestation. In contrast to the ACCESS study we did not observe any gender bias. In addition, there are notably differences in the clinical course of patients with pulmonary sarcoidosis compared with their extrathoracic counterparts. Pulmonary sarcoidosis is often incidentally diagnosed, whereas all isolated extrathoracic variants in our cohort showed a (per-) acute and sometimes recurrent disease. Despite substantial enlargements of salivary glands or lymph nodes, patients denied any tenderness on palpation.

Enlargements of major salivary glands and lymph nodes were also common in SS, which affects ~1% of the adult population [1]. Parenchymatous lesions of the parotid gland occur in both sarcoidosis and SS. MALT lymphoma should be excluded by open biopsy when enlarged intra-parotideal lymph nodes are diagnosed in SS (Fig. 3) [19]. It has been estimated that MALT lymphoma originates in 5-10% of primary SS [1]. As expected, sicca symptoms of the eyes and mouth occurred in all patients due to a dysfunction of minor and major salivary glands. Since sicca symptoms occur in a substantial proportion of sarcoidosis (27.8%), early disease stages of SS are especially hard to distinguish. The mean age at diagnosis for SS was 56.8 years, with a striking female predominance of ~8:1. Despite a well-defined symptomatology, time to diagnosis was ~21 months. There may be some explanations for these contradictory results: (i) sicca symptoms are common in an ageing population; (ii) coincidence with anti-cholinergic drugs; (iii) sicca symptoms misinterpreted as effects of the menopause by middle-aged women; (iv) lack of symptom specificity; and (v) lack of disease burden at early stages [1].

In fact, the lack of symptom specificity remains the main problem in H&N rheumatology. Major salivary glands and cervical lymph nodes represent hot spot lesions in the H&N involvement. Rheumatic disorders contribute 3.4% of all glandular enlargements not obviously related to a neoplastic disease, or 4.2% from a total of 545 patients with undetermined lymphadenopathy. These data highlight the clinical evidence of H&N involvement in rheumatic diseases.

This prompted us to establish a simple but effective diagnostic pathway to reduce the count of undiagnosed cases. Based on our findings, a rheumatic disorder has to be considered in patients with a substantial discrepancy between distinct clinical findings and a quite moderate symptomatology. In particular, undetermined involvement of salivary glands and lymph nodes, undetermined sinonasal impairment with a possible coincidence of otological symptoms might be seen as hints of a rheumatic disorder. Beside differentiated laboratory tests, the histological proof remains the gold standard in cases of H&N sarcoidosis or granulomatosis with polyangiitis.
Nasal biopsy was performed in granulomatosis with polyangiitis, US-assisted glandular biopsy or lymph node extraction was done in sarcoidosis, respectively. Due to the ACR criteria minor salivary gland biopsy is not obligatory in the diagnostic procedure of SS. However, our data point out that SS can be hardly distinguished from sarcoidosis, especially in early disease stages. Thus, sublabial mucosal salivary gland biopsy remains a meaningful diagnostic tool. After introduction of this diagnostic pathway in 2008, the number of newly diagnosed cases increased 5-fold, emphasizing our hypothesis that H&N rheumatic disorders are dramatically underestimated.

Altogether, rheumatic disorders of the H&N are underrepresented due to less specific symptoms and a variable clinical appearance. However, most of these diseases contribute to three major disorders (SS, granulomatosis with polyangiitis and sarcoidosis, respectively) with few cardinal symptoms. A simple diagnostic pathway reduces the number of undiagnosed cases. Prospective multicentre studies are necessary for a full assessment of the clinical profile of H&N rheumatic disorders.

**Rheumatology key messages**

- Rheumatic disorders of the H&N are underrepresented due to less specific symptoms and a variable clinical appearance.
- Standardized diagnostic pathways help to distinguish between neoplastic, infectious and rheumatic diseases.

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**References**