ORIGINAL INVESTIGATIONS

Diseases with major salivary glands enlargement and orbits, nose and paranasal sinuses lesions in the practice of a rheumatologist

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Objective: *to analyze the nosological spectrum, demographic, clinical and laboratory characteristics of diseases with a significant enlargement of major salivary (SG) / lacrimal glands, and/or accessory organs of the eye and paranasal sinuses lesions in rheumatological practice.*

Patients and methods. *This work includes 73 patients who underwent a complex clinical and laboratory, imaging, pathomorphological and histomolecular examination, which was necessary to establish a nosological diagnosis. In all cases, the diagnosis was confirmed pathomorphologically.*

Results and discussion. *Sjogren's syndrome (SjS) was diagnosed in 30 (41%) patients (14 of them developed lymphoproliferative disorder, LPD, as a complication), granulomatosis with polyangiitis (GPA) – in 12 (16.4%), IgG4-related disease (IgG4-RD) – in 10 (13.7%), sarcoidosis – in 6 (8.2%), non Langerhans cell histiocytosis – in 2 (2.7%), AL-amyloidosis – in 1 (1.4%), Warthin's tumor – in 1 (1.4%), chronic atrophic rhinitis – in 1 (1.4%), infectious lesions – in 3 (4.1%) (HIV-associated – in 2, dirofilariasis – in 1), idiopathic inflammatory pseudotumor – in 6 (8.2%). In 1 (1.4%) patient, the diagnosis could not be established.*

A massive increase of major SG was observed in 46 patients, more often (in 28 cases) with SjS with LPD or without it, with IgG4-RD (in 7) and sarcoidosis (in 6). Orbital lesions were observed in 18 patients: in 7 with IgG4-RD, in 5 with idiopathic inflammatory pseudotumor, in 2 with sarcoidosis, in 2 with GPA, and in 1 each with non Langerhans cell histiocytosis and dirofilariasis. Nasal lesions in the form of chronic rhinosinusitis with or without nasal septum perforation, were found in 18 patients, 12 of whom suffered GPA and 6 – IgG4-RD.

Two algorithms, that can facilitate the choice of additional studies and the direction of diagnostic search have been proposed for practicing rheumatologists.

Conclusion. *Taking into account the possible similarity of clinical manifestations of the diseases with the formation of mass-like tissue, the differential diagnosis should be based on pathomorphological study.*

Key words: *salivary glands enlargement; lacrimal glands enlargement; Sjogren's syndrome; IgG4-related disease; granulomatosis with polyangiitis; sarcoidosis; MALT-lymphoma.*

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Patients with "unclear" diagnosis and systemic manifestations are often referred to a rheumatologist to exclude or confirm rheumatic disease (RD). In cases of multiple organ lesions, the presence of skin manifestations or involvement of the osteoarticular system, patients turn to a rheumatologist early enough, however, with lesions (especially isolated) of the major salivary glands (SG), eyes, paranasal sinuses, patients are observed for a long time by different specialists, often without a certain diagnosis, receiving insufficiently effective local treatment.

The main RDs, occurring with lesions of the major SG, orbital organs and paranasal sinuses, are ANCA-associated vasculitis, Sjogren's syndrome (SS), and IgG4-related disease (IgG4-RD). At the same time, the spectrum of nosologies in which these organs are affected is very wide and includes oncological and oncohematological diseases, infectious processes, granulomatous diseases, etc. [1, 2] Differential diagnosis often requires a large number of tests and a multidisciplinary approach.

The aim of this study is to analyze the nosological spectrum, as well as demographic and clinical and laboratory characteristics of diseases with a significant increase in the major salivary (SG) / lacrimal glands, lesions of the accessory apparatus of the eye and paranasal sinuses in rheumatological practice.

Patients and methods. In years 2019 – 2021 86 primary patients with a significant increase of major SG / lacrimal glands, lesions of accessory apparatus of the eye, nose and/or paranasal sinuses turned for an outpatient appointment at the clinical diagnostic center of the V.A. Nasonova Research Institute of Rheumatology (lab of intensive therapies). The study included 73 patients for whom the results of all examinations necessary for establishing a nosological diagnosis were available. The study was conducted in a real clinical practice. The scope of laboratory and visualization tests, additional consultations of specialists were determined individually in each case.

Clinical and laboratory data. Clinical, biochemical and immunological (antinuclear factor – ANA – measured by indirect immunofluorescence on human Hep-2 cells, antibodies to SS-A/Ro, SS-B/La, ANCA screen, cANCA, pANCA, antibodies to double-stranded DNA measured by enzyme immunoassay, rheumatoid factor – RF – IgM, highly sensitive CRP, C3/C4 complement compounds, IgG, IgG4, IgM, IgA, IgE, measured by immunonephelometric method) blood tests, protein electrophoresis, general urine analysis were performed in all patients in the biochemical laboratory of the V.A. Nasonova Research Institute of Rheumatology.

Table 1. Nosological diagnoses in patients with enlargement of major SG, orbital organs and lesions of the nose and paranasal sinuses, n (%)

Symptom	Total	GPA	IgG4-RD	SS	SS + lymphoma	Sarcoidosis	Other
Lesions of the nose/sinuses	24	12 (50)	6 (25)	2 (8.3)	0	0	4 (16.7)
Orbital lesions	18	2 (11.1)	7 (38.9)	0	0	2 (11.1)	7 (38.9)
SG enlargement	46	0	7 (15.2)	14 (30.4)	14 (30.4)	6 (13)	5 (10.9)
Lesions of the nose + orbits	3	2 (66.7)	1 (33.3)	0	0	0	0
Lesions of the nose + SG	1	0	0	0	0	0	1 (100)
SG enlargement + orbits	5	0	3 (60)	0	0	2 (40)	0
Lesions of the nose + orbits + SG	3	0	3 (100)	0	0	0	0

Immunochemical evaluation of blood serum and urine for the detection of monoclonal proteins were performed in the laboratory of humoral immunity of the National Medical Research Center of Hematology, dental examination (sialometry, sialography, biopsy of the small SG of lower lip) and ophthalmological examination (Schirmer test , Norn's test, staining of the corneal epithelium with fluorescein and Rose Bengal) – at the V.A. Nasonova Research Institute of Rheumatology.

Visualization. Computed tomography (CT), including multispiral CT, and / or magnetic resonance imaging (MRI) of the thorax, abdomen, sinuses, and orbits have been performed in different hospitals. The presence and degree of increase in large SG was assessed by visual examination and palpation. The presence of enlargement of the lacrimal glands and / or extraocular muscles in all cases was confirmed by CT or MRI.

Pathological and molecular studies. All patients with an increase in SG, orbits (including the lacrimal gland), and lymph nodes (LN) underwent histological and immunohistochemical (IHC) examination of tissue biopsies of these organs in the Department of Pathological Anatomy of Human Tumors of the N.N. Blokhin Russian Cancer Research Center and / or in National Medical Research Center of Hematology. The diagnosis of lymphoma was established only in the presence of histological and IHC confirmation.

B-cell clonality in fresh frozen tissue and / or paraffin embedded blocks was assessed by polymerase chain reaction (PCR) using IgVH gene rearrangements at the laboratory of molecular hematology of the National Medical Research Center of Hematology. If B-cell clonality was detected in the absence of histological signs of lymphoma formation, the diagnosis of lymphoproliferative disease (LPD) was rejected.

The scope of research was determined by the attending physician, depending on the clinical situation.

For the diagnosis of SS, the Russian diagnostic criteria were used [3], for IgG4-RD – comprehensive diagnostic criteria, H. Umehara 2011. [4] , LPD – WHO classification.

Statistical methods. Data analysis was performed using MS Excel 2013. Qualitative data are presented as absolute and relative frequencies (expressed as a percentage), quantitative data are presented as mean (M) with standard deviation (_).

Results. SS was diagnosed in 30 (41%) patients, 14 of whom had a complication of LPD, and 9 – the development of MALT tissue in the SG without a clear histological picture of LPD (despite the positive B-cell clonality according to PCR data in some patients). In 3 of these cases a combination of SS with rheumatoid arthritis was revealed (in 2 patients with SS and lymphoma and in 1 with nasal lesions), in 1 patient – SLE, and in 1 patient – limited form of scleroderma (in both cases, MALT tissue in SG was detected). The remaining patients were diagnosed with granulomatosis with polyangiitis (GPA) – in 12 (16.4%), IgG4-RD – in 10 (13.7%), sarcoidosis – in 6 (8.2%), non-Langerhans cell histiocytosis – in 2 (2.7%), AL-amyloidosis – in 1 (1.4%), Worthin's tumor – in 1 (1.4%), chronic atrophic rhinitis – in 1 (1.4%), infection in 3 (4.1%; HIV-associated – in 2, dirofilariasis – in 1), idiopathic inflammatory pseudotumor (iIP) – in 6 (8.2%). In 1 patient, the diagnosis was not established, despite the full range of studies, repeated biopsy and consultations of related specialists. The diagnoses of patients with enlargement of major SG, orbital organs and lesions of the nose and paranasal sinuses are presented in Table. 1.

A massive enlargement of major SG was found in 46 patients. These were mostly patients with SS (n = 28), 14 of whom had lymphoproliferative complications: 13 – combination of SS with MALT lymphoma and 1 – SS with diffuse large B-cell lymphoma. At the same time, in half of the observations, where diagnosis was newly established at the V.A. Nasonova Research Institute it was already at the stage of formation of lymphoproliferative complications. Further, according to the frequency of lesions of major SG followed: IgG4-RD (15.2%) and sarcoidosis (13%). Rarer (10.9%) reasons for SG enlargement were: tumors (Worthin's tumor), AL-amyloidosis, non-Langerhans cell histiocytosis, HIV-associated diffuse infiltrative lymphocytosis, and sialoadenitis in iIP.

In 39 patients, there was enlargement of the parotid SG (PSG), in 13 – of submandibular SG (SMSG), in 8 – of sublingual SG. In the vast majority of cases, the enlargement of SG was bilateral, firm on palpation. In 5 patients with high SS activity (severe hypergammaglobulinemia and extra glandular manifestations), there was a minor enlargement of SG. Since there were no signs of a poor prognosis for the development of LPD [5], biopsies were not performed in these patients. All other patients were referred for biopsy of SG and / or enlarged LN.

Comparative demographic, clinical and laboratory characteristics of patients with different nosological diagnoses and enlarged major SG are presented in table. 2.

Patients diagnosed with LPD were generally older and had a longer duration of symptoms. Only 3 out of 14 patients previously received therapy: 3 patients – low doses of glucocorticoids

Table 2. Demographic, clinical and laboratory characteristics of patients with different nosological diagnoses and an enlarged major SG

Feature	SS + LPD (n = 14)	SS + MALT-tissue (n = 9)	IgG4-RD (n = 7)	Sarcoidosis (n = 6)
Men / women, n	2/12	0/9	2/5	2/4
Age at the time of treatment, years, M±σ	57.6 ± 12.8	49.4 ± 11.2	45.6 ± 8.4	41.2 ± 7.6
Duration of symptoms, months M±σ	101.4 ± 61.1	40.2 ± 25.2	47.1 ± 31.6	12 ± 9.6
Dry mouth symptoms	++ / +++	++ / +++	+/-	+++
Bilateral enlargement of SG, n	13	7	7	6
Systemic course, n	3	3	7	7
Lack of antecedent immunos uppressive active therapy, n	11	7	N / a	N/a
Anti-Ro +, n	12	8	0	0
ANA Hep2> 1/320, n	14	9	0	0
Increased serum IgG4 > 2 N, n	0	0	7	0
Tissue clonality (PCR), n	13	4	0	Not detected
Histology	Confirmed LPD	Formation of MALT tissue without signs of LPD and restriction by κ/λ	Morphological signs of IgG4-RD [6], the formation of MALT tissue	Sarcoid granulomas

Note. N/a – not applicable; here and in table. 3: n/d – not determined; N – normal.

(GC) and methotrexate up to 10 mg / week, 1 – low doses of oral GCs, and 1 – medium doses of oral GCs and cyclophosphamide for vasculitis due to SS. B-cell clonality by PCR was detected in almost half of patients with MALT tissue in SG, however, histological and IHC studies did not confirm the presence of LPD.

An enlargement of SG in sarcoidosis was present in the systemic course of the disease: in all 6 cases PSG were involved, in 2 – in combination with SMSG, and in 1 – all three pairs of major SG, which was accompanied by the rapid development of severe sicca symptoms. In all patients, additional examination revealed lesions of the lungs and intrathoracic lymphadenopathy, and in 2 – lesions of the parenchymal abdominal organs as well. In all cases, the diagnosis was confirmed by histological examination of biopsy specimens of SG or LN.

Orbital lesions most often occurred in IgG4-RD (7 patients) and iIP (in 5 out of 6). In IgG4-RD, the lesions of the orbits were symmetrical; in all patients, both the lacrimal glands and extraocular muscles were involved. In 6 out of 7 patients with IgG4-RD, there was a simultaneous enlargement of SG and lacrimal glands, and in 3 – also nasal lesion (recurrent polysinusitis). The diagnosis of IgG4-RD was verified by biopsy of the lacrimal gland in 3 patients. With iIP, the lesion of the orbits was often unilateral with pronounced asymmetry, in 3 out of 5 patients there was a massive thickening of extraocular muscles in the absence of signs of dacryoadenitis, which was accompanied by unilateral exophthalmos and diplopia, in 1 of these patients retrobulbar localization of the pseudotumor was also found. Endocrine ophthalmopathy was excluded in all patients. Histological examination, along with moderate fibrotic tissue changes, revealed a polyclonal lymphoid infiltrate with plasma cells and the absence or secretion of IgG4 onlyin single cells. Signs of orbital lesion were also present in 2 patients with sarcoidosis and in 2 patients with GPA (including 1 patient with bone destruction of the lower orbital wall). The main clinical and laboratory characteristics of patients with orbital lesions are presented in table. 3.

In addition to the cases described above, a massive lesion of periorbital tissues of the xanthelasma type was observed in a patient with non-Langerhans cell histiocytosis and orbit lesion due to rare transmissive helminthiasis – dirofilariasis. Nose involvement was manifested by chronic rhinosinusitis (in 18 patients) with perforation of the nasal septum (in 13) and the formation of a saddle deformity (in 5) or without it. At the same time, in 2 patients with SS, isolated perforation of the nasal septum was revealed in the setting of chronic atrophic rhinitis and vasculitis in the absence of paranasal sinuses damage. Two patients had nasal cavity lesions of IgG4-related pseudotumor type and non-Langerhans cell histiocytosis. In 1 patient, perforation of the nasal septum occurred in the course of otolaryngological disease.

In patients with both GPA and IgG4-RD, nasal lesions were observed at the onset of the disease, however, with GPA it proceeded more aggressively, with the formation of rough crusts, recurrent bleeding and the formation of bone defects and deformities (of the saddle type). In GPA, in contrast to IgG4-RD, rhinosinusitis was accompanied by a significant increase in the CRP level (more than 3 norms) and leukocytosis in the peripheral blood. All of these patients during examination at the V.A. Nasonova Research Institute of Rheumatology had ANCA to proteinase 3 (PR3). Only in 2 out of 12 patients, GPA was newly diagnosed at the V.A. Nasonova Research Institute of

Table 3. Basic clinical and laboratory characteristics of patients with orbital lesions, n

Symptom	IgG4-RD (n = 7)	GPA (n=2)	Sarcoidosis (n= 2)	iIP (n=5)
Экзофтальм	0	2	0	3
Bilateral lesions	7	0	2	2
Dacryoadenitis	7	0	2	2
Eye sicca symptoms	- / +	-	++	+/-
Nasal congestion	5	2	0	0
Crusts in the nose	0	2	0	0
Nasal hemorrhage	0	2	0	0
Bone destruction	0	2	0	0
CRP level	N	>5 N	N	N
Increased serum IgG4 level	7/7	0	Not detected	0
Histology	Morphological signs of IgG4-RD [6]	Necrotizing vasculitis, granuloma formation	Sarcoid granulomas	Fibrosis and sclerosis of tissues, nonspecific lymphoid infiltrate, absence of granulomas, necrosis or κ/λ restriction

Rheumatology, therefore, the interpretation of the causes of rhinosinusitis in half of the cases did not cause clinical difficulties and did not require differential diagnosis.

Massive destruction of the nasal bones, hard and soft palate were detected in 1 patient with HIV-associated opportunistic infection (mycosis). In 1 patient, the diagnosis could not be established.

Discussion. Although the spectrum of diseases manifested by an enlargement of major SG and orbital organs is broad, their clinical manifestations may at first glance be similar: the appearance of a tumor-like lesion of the glands, often accompanied by the development of different degree of dryness. A thorough differential diagnosis is absolutely necessary for the timely administration of therapy and prevention of the development of severe complications.

Our study reflects the real outpatient practice of a rheumatologist, therefore, not all patients underwent the entire possible complex of tests and, unfortunately, not all indicators were comparable to the same extent. At the same time, V.A. Nasonova Research Institute of Rheumatology is the center where the most complex and severe RD cases are accumulated, including those with lesions of the SG, orbits and nose / paranasal sinuses, so we were able to examine and evaluate a large group of patients in a short time. The aim of this study did not include a detailed description of each nosology; rather, we tried to present a general picture, highlighting only the most common causes of lesions in SG, orbits and ear-nose-throat (ENT) organs in real rheumatological practice. Based on the analysis of the reasons for the enlargement of major SG, orbital organs and lesions of the ENT organs, two algorithms were formulated that will facilitate the choice of additional studies and the direction of diagnostic search for practicing rheumatologists (Fig. 1, 2).

Pathological examination is the leading diagnostic method, however, it is possible to assume diagnosis in most cases based on the clinical and laboratory signs of the disease. In systemic RD, enlargement of SG and lacrimal glands is most often bilaterally symmetric. As shown by the results of this and our previous studies [7], SMSG are more often involved in IgG4-RD, which is consistent with the data of foreign authors [8, 9], and, of course, in AL-amyloidosis [10]. In all of our patients with unilateral increase in SG, except for 1 patient, an alternative diagnosis (tumor, histiocytosis) was confirmed, therefore, in all cases of unilateral enlargement of SG or lacrimal gland biopsy is required.

In this study, the most common diagnosis was SS. It is noteworthy that in almost half of the patients this diagnosis was first verified at the V.A. Nasonova Research Institute of Rheumatology and at that time they already had lymphoproliferative complications. In some patients, SS is associated with anticentromere antibodies. As we have shown earlier, in such cases, "classic" anti-Ro / La antibodies may not be detected [11], which additionally may complicate timely diagnosis. The majority of patients with lymphoma and massive SG enlargement due to MALT tissue formation had not previously received any therapy, and this could significantly affect the development of lymphoproliferative complications. In addition, the emergence of B-cell clonality in tissues is also one of the reasons for the formation of LPD [5], it is likely that such patients should receive more intensive therapy with anti-B-cell drugs and / or cytotoxics.

Lesions of the nose with bone-destructive changes are characteristic primarily of systemic necrotizing ANCA-associated vasculitis, which is confirmed by the data of our study. At the same time, there are very few descriptions of bone-destructive lesions and "median lethal granuloma" type lesions in IgG4-C3 [12–14]. Unfortunately, almost all patients with nasal lesions and GPA were admitted to our center at the stage of extensive systemic vasculitis, with multiple organs involvement and often with an already established diagnosis of GPA. In this regard, data on the early differential diagnosis of rhinitis could not be obtained.

Interestingly, in contrast to lesions of the SG and the nose, in almost a third of cases of orbital involvement, it was not possible

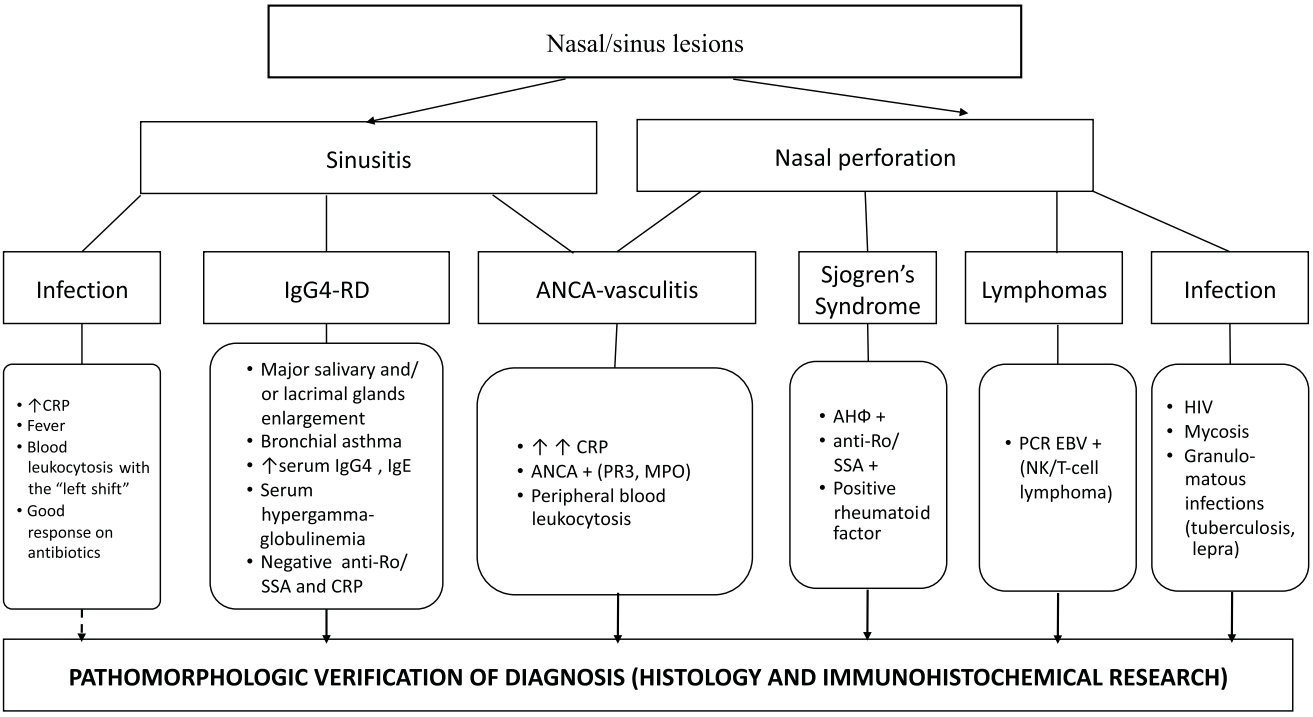

Fig. 1. *Algorithm for differential diagnosis of diseases with nose / paranasal sinuses lesions. MPO – myeloperoxidase*

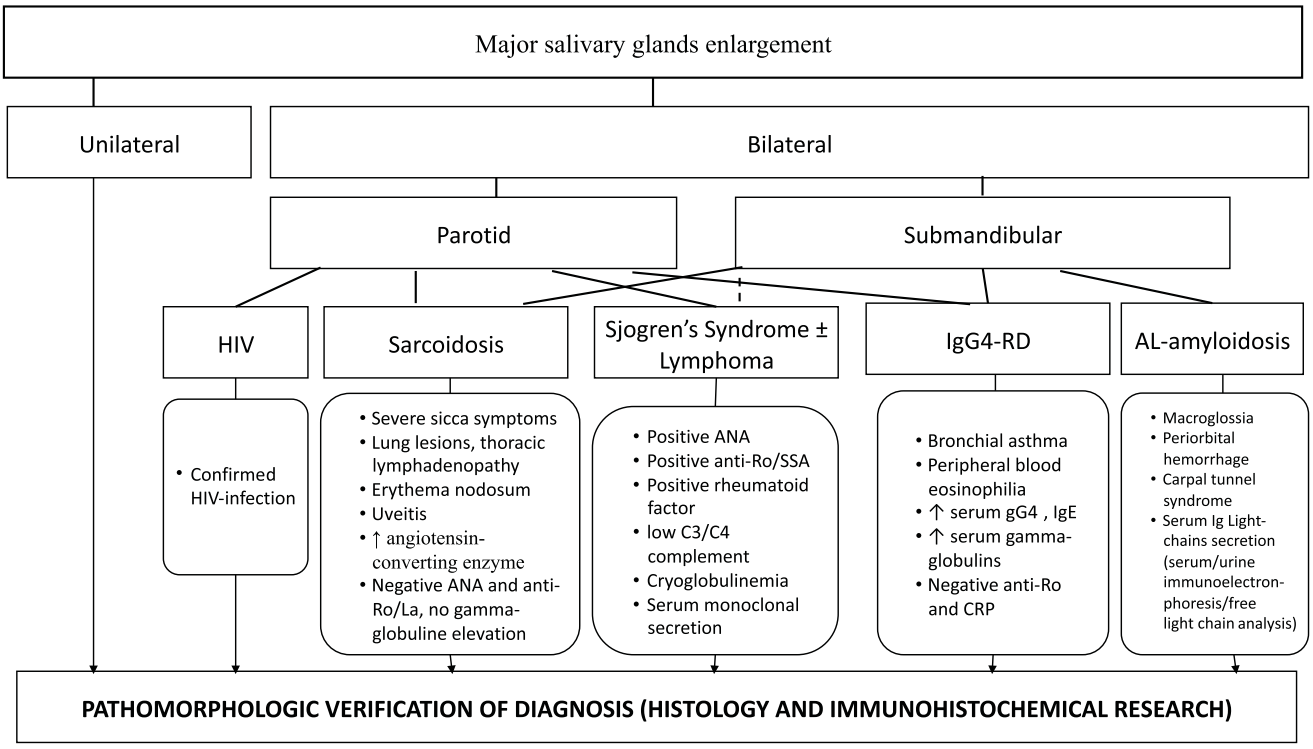

Fig. 2. *Algorithm for differential diagnosis of diseases with SG enlargement. АПФ – angiotensin converting enzyme*

to establish a definite nosological diagnosis. In our study, 5 (26%) of 19 patients had orbital mass, which was accompanied by a vivid clinical picture with the development of exophthalmos and visual impairment in some cases, while the histological examination was inconclusive, and the diagnosis was formulated as "inflammatory pseudotumor of the orbits". The management of such patients is fraught with great difficulties, since, on the one hand, the absence of a specific nosological diagnosis entails a refusal to

prescribe immunosuppressive therapy, and on the other hand, patients with massive thickening of extraocular muscles often have much worse therapeutic response than, for example, patients with IgG4-RD, and are steroid-resistant.

We also observed patients with infectious diseases, in particular with HIV-associated lesions. Of interest is the case of a symmetric massive PSG enlargement (HIV-associated diffuse infiltrative lymphocytosis) and extensive necrotic lesions of the nasal cavity and pharynx due to an opportunistic fungal infection. Presently, the situation with this infection in Russia is unfavorable, and a larger number of such patients can be expected. Both the asymptomatic secretion of autoantibodies in HIV-infected patients and the combination of this infection with various RD and, of course, with LPD have been described [15, 16].

Conclusion. Taking into account the possible similarity of clinical manifestations, diseases presenting with the mass formation should be differentially diagnosed on the pathomorphological bases.

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Conflict of Interest Statement

The investigation has been conducted within scientific topic №AAAA-A19-119021190145-2 «Multimodal approaches to the choice of innovative therapy for systemic connective tissue diseases».

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