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THE CLINICAL IMPLICATION OF NASAL BIOPSY FOR CLASSIFYING GRANULOMATOSIS WITH POLYANGIITIS IN PATIENTS WITH RHINOSINUSITIS: A SINGLE CENTRE RETROSPECTIVE STUDY

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Background: Granulomatosis with polyangiitis(GPA) mainly involves the upper and lower respiratory tracts and kidneys and induces necrotising vasculitis and granuloma. Nasal biopsy has been recommended in GPA-suspected patients to not only completely cure chronic rhinosinusitis, but also clearly discriminate its aetiologies.

Objectives: We investigated whether the classification of GPA could be made without nasal biopsy in immunosuppressant drug-naïve 45 patients with chronic rhinosinusitis who had previously been classified as GPA.

Methods: We retrospectively reviewed the medical records of 45 patients with GPA. Twenty-six patients exhibited chronic rhinosinusitis, among which 16 patients underwent nasal biopsy (10 with granuloma and 6 without granuloma). We applied the 2007 European Medicines Agency algorithm for the classification of GPA, the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis and the 2017 American College of Rheumatology/European League Against Rheumatism provisional classification criteria for GPA to them for reclassifying GPA. (Figure1)

Results: The mean age was 58.4 years and 17 patients were men. There were no differences in clinical and laboratory results between those with and without granuloma. Among 6 patients without granuloma on nasal biopsy, 3 patients with only ANCA and chronic rhinosinusitis could be classified as GPA due to PR3-ANCA (or C-ANCA) positivity. Among 9 patients without nasal biopsy, 3 patients with only chronic rhinosinusitis could be classified as GPA due to GPA-specific lung lesions. (Table 1) When we excluded an item of granuloma in 10 GPA patients with granuloma on nasal biopsy, 4 patients without ANCA could be classified as GPA due to GPA-specific lung lesions and cartilaginous involvement. (Table 2)

Figure1. The algorithm for GPA patients with chronic rhinosinusitis

Table1 Fulfillment of the 2007 ERM algorithm and the 2017 ACR/EULAR provisional criteria in 9 patients with chronic rhinosinusitis and without nasal biopsy

Patient number	PR3-ANCA or C-ANCA	MPO-ANCA or P-ANCA	GPA surrogate marker (the 2007 ERM algorithm)	Positive item (score) (the 2017 ACR/EULAR provisional criteria)	Total score
1	Yes	No	Chronic sinusitis, Septal perforation	Sino-nasal congestion (3), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), Nodule on Chest imaging (2)	12
2	Yes	No	Chronic sinusitis, Nasal crust	Sino-nasal congestion and nasal crusting (3), PR3-ANCA (or C-ANCA) (5)	8
3	No	Yes	Chronic sinusitis, Septal perforation	Sino-nasal congestion (3), Cartilaginous involvement (2), Nodule on Chest imaging (2)	7
4	Yes	No	Chronic sinusitis, Subglottic stenosis	Sino-nasal congestion (3), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), Nodule on Chest imaging (2)	12
5	Yes	No	Chronic sinusitis, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), PR3-ANCA (or C-ANCA) (5)	9
6	No	Yes	Chronic sinusitis	Sino-nasal congestion (3), Nodule on Chest imaging (2)	5
7	No	Yes	Chronic sinusitis	Sino-nasal congestion (3), Nodule on Chest imaging (2)	5
8	Yes	No	Chronic sinusitis	Sino-nasal congestion (3), PR3-ANCA (or C-ANCA) (5), Nodule on Chest imaging (2)	10
9	Yes	No	Chronic sinusitis, Subglottic stenosis	Sino-nasal congestion (3), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5)	10

Table2 Reassessment of the fulfillment of the 2007 ERM algorithm and the 2017 ACR/EULAR provisional criteria in 10 patients with chronic rhinosinusitis and granuloma on nasal biopsy

Patient number	PR3-ANCA or C-ANCA	MPO-ANCA or P-ANCA	GPA surrogate marker (the 2007 ERM algorithm)	Positive item (score) (the 2017 ACR/EULAR provisional criteria)	Total score
1	No	Yes	Chronic sinusitis, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), Nodule on chest imaging (2)	6
2	No	No	Chronic sinusitis, Nasal crusting, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), Nodule on chest imaging (2)	6
3	Yes	No	Chronic sinusitis, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5), Nodule on chest imaging (2)	13
4	Yes	No	Chronic sinusitis, Hoarseness	Sino-nasal congestion (3), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5)	10
5	No	No	Chronic sinusitis, Septal perforation	Sino-nasal congestion (3), Cartilaginous involvement (2), PR3-ANCA (or C-ANCA) (5)	10
6	Yes	No	Chronic sinusitis, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), PR3-ANCA (or C-ANCA) (5), Nodule on chest imaging (2)	11
7	No	No	Chronic sinusitis, Septal perforation	Sino-nasal congestion (3), Cartilaginous involvement (2)	5
8	No	No	Chronic sinusitis	Sino-nasal congestion (3), Nodule on chest imaging (2)	5
9	No	No	Chronic sinusitis, Nasal crusting, Otitis media	Sino-nasal congestion (3), Hearing reduction (1), PR3-ANCA (or C-ANCA) (5), Nodule on chest imaging (2)	11
10	No	Yes	Chronic sinusitis, Nasal crusting	Sino-nasal congestion (3), Nodule on chest imaging (2)	5

Conclusion: Nasal biopsy is necessary and useful for classifying GPA. However, nasal biopsy could be replaced with PR3-ANCA (or C-ANCA) positivity, GPA-specific lung lesions and cartilaginous involvement in GPA suspected patients with chronic rhinosinusitis.

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Epidemiology, risk factors for disease or disease progression

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SERUM CXCL13 LEVELS ARE ASSOCIATED WITH LYMPHOMA RISK AND LYMPHOMA OCCURRENCE IN PRIMARY SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by an increased risk for non-Hodgkin lymphoma (NHL) development. Ectopic germinal center (GC) formation in the salivary gland (SG) epithelium of pSS patients is thought to be associated with high risk for pSS-associated NHL. The chemokine (C-X-C motif) ligand 13 (CXCL13) is a major chemoattractant for B cell migration into the GC, plays an important role in the organization of B cell follicles, and enhances BCR-triggered B cell activation. The increased B cell activation within ectopic GC may lead to excessive B cell proliferation and along with genetic abnormalities may drive the transition from the early clusters of GC B cells through oligoclonal and later monoclonal B cell expansion to lymphoma.

Objectives: To investigate the potential of CXCL13 as a biomarker to assess NHL risk in pSS.

Methods: Serum CXCL13 concentrations were quantified by ELISA in 48 healthy individuals, 165 pSS patients without NHL and 38 pSS patients with NHL from the United Kingdom Primary Sjögren's Syndrome Registry (UKPSSR). Among these patients, follow-up serum samples from 83 and 11 patients without and with NHL respectively were available and CXCL13 measured. PSS patients without NHL were stratified into low risk (LR), moderate risk (MR) and high risk (HR) groups according to the lymphoma risk assessment tool proposed by Fragkioudaki et al, 2016. Differences in CXCL13 levels among risk groups were analyzed using the Mann-Whitney test and differences in CXCL13 levels between initial (visit 1) and follow-up (visit 2) samples were measured by repeated measures MANOVA. Associations of CXCL13 with B cell markers were determined by Pearson correlation. Logistic regression analyses were performed to model the NHL risk against CXCL13 concentrations.

Results: At visit 1, there were 24 LR, 58 MR and 1 HR pSS patients. Because of the small sample size of the HR "group", it was excluded from further analyses. Serum CXCL13 levels were higher in all pSS groups compared to healthy controls ($p < 0.0001$), and the levels in patients with a history of NHL were higher compared to those without ($p = 0.0311$). Visit 1 LR patients had significantly lower CXCL13 levels than MR patients ($p = 0.0015$) and pSS patients with NHL ($p = 0.0017$). Serum CXCL13 levels remained stable between visit 1 and visit 2 (mean time between visits = 4 years) for all pSS groups. CXCL13 was associated with B cell markers, including Immunoglobulin G (IgG) ($p = 0.0014$), B-cell activating factor ($p < 0.0001$), beta-2 microglobulin ($p < 0.0001$), combined free light chains ($p < 0.0001$), κ light chain ($p < 0.0001$), λ light chain ($p = 0.0002$), κ -to- λ ratio ($p = 0.0013$), and Anti-SSA/Ro autoantibodies ($p = 0.0005$). Finally, serum CXCL13 levels, age, IgM, IgA, and white blood cell count were independent predictors of NHL risk score in pSS.

Conclusion: Our findings have demonstrated that serum CXCL13 levels were elevated in pSS patients with NHL and MR pSS patients compared to LR pSS patients and remained stable between visit 1 and visit 2. CXCL13 was an independent determinant of NHL risk score and could potentially be used as an additional NHL risk biomarker in pSS.