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Central nervous system involvement in granulomatous polyangiitis (GPA)

O. Karadağ, O. Helvaci, I. Dogan, U. Kalyoncu, A. Akgogan, L. Kılıc, S. Kiraz
Hacettepe University, Ankara, Turkey

Introduction.– Even though granulomatous polyangiitis (GPA) is a multisystem autoimmune disorder, the central nervous system (CNS) involvement is an uncommon manifestation. The aim of this study was to evaluate CNS involvements of patients with GPA.

Patients.– The hospital files of the patients with the diagnosis of GPA who were followed up between the years 2005 and 2012 in Hacettepe University Hospital were retrospectively evaluated.

Results.– Totally 48 patients (M/F: 27/21) were evaluated. Mean ages and disease duration was 42.6 ± 10.4 and 4.2 ± 3.3 years. CNS involvement was seen in three (6.3%) patients.

First case was a 67 years old female presented with constitutional symptoms, anemia and headache. Multiple parenchymal metastasis were found in Torax CT and brain MRI (cerebellar and left temporal region). PET-BT revealed lesions in thoracic, sinonasal and cranial regions. Malignancy was not detected in tru-cut lung biopsy. cANCA and MPO were positive. After pulse therapy (MP and CYC) symptoms regressed.

Second case was a 55 years old female presented as pititus and sinopulmonary symptoms. Brain MR revealed a frontal mass involving bilaterally olfactory bulb. Imaging and pathologic evaluation of parasellar region was consisted with GPA. After pulse MP and CYC findings decreased.

First case as a male patient presented with uveitis, sinopulmonary involvement and sensorimotor neuropathy. He was treated with pulse therapy (MP and CYC) + IVIG. After one year, pan sinusitis, fever and headache. While he was on maintenance therapy he had fever, vision loss and headache. There was frontal abscess in brain MR. Even though infective endocarditis was diagnosed and antibiotic therapy was started he had been exitus after 3 days.

Discussion.– CNS involvement in GPA is an infrequently seen. In addition to disease related etiology (contiguous invasion of granuloma from extracranial sites, remote intracranial granuloma, and CNS vasculitis), infectious complications related to immunosuppressive drugs might be seen as CNS involvement.

Reference
[1] Oz balkan Z et al. Wegener’s granulomatosis: clinical and laboratory work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up for idiopathic subglottic stenosis should always include an infectious work-up. Curr Rheumatol 2006;25:358-63.

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P75

Clinical manifestations of granulomatosis with polyangiitis (Wegener’s granulomatosis) in the upper respiratory tracts

O. Iaremenko, L. Petelytska
NMU, Kiev, Ukraine

Introduction.– Subglottic stenosis affects 10 to 20% of patients with granulomatosis with polyangiitis (GPA). It is potential life-threatening complication and may be the initial symptom of GPA. Therefore, the work-up for idiopathic subglottic stenosis should always include an evaluation for GPA.

Methods.– Case presentation.

Results.– A 36-year-old female with relapsing idiopathic subglottic stenosis was supervised by otolaryngologist during 3 years. Patient had no other systemic symptoms and laboratory abnormalities. Flexible laryngoscopy detected circumferential narrowing of the subglottis. An upper respiratory tract biopsy revealed vasculitis and necrosis. Two endoscopic subglottic dilations were performed. In December 2011, patient was admitted to our hospital with migratory oligoarthritis, nasal stuffiness, rhinitis with bloody crusts, hoarseness, stridor, dyspnea on exertion. Joint tenderness and swelling, cutaneous extravascular necrotizing granulomas over the extensor surface of the olecranon region, digitals infarctions, papules on the neck area were found on physical examination. There were elevation of ESR (25 mm/hour) and positive PR3-ANCA. CT scan showed granulomatous lesions in paranasal cavities. Patient was diagnosed with GPA, and was treated with oral methylprednisolone (mPSL) (24 mg/day) and interriment cyclophosphamide (200 mg twice weekly intramuscular). All manifestations improved and ESR became within normal limit. When the dose of mPSL had been tapered to 13 mg/day (after 7 months) cutaneous extravascular necrotizing granulomas, rhinitis and subacute onset of respiratory stridor developed. Rituximab was administered due to the relapse of subglottic stenosis.

Conclusion.– Chronic or subacute subglottic stenosis could be seen in GPA and might precede other organ involvement. The treatment of subglottic stenosis of GPA requires multidisciplinary management by the rheumatologist, otolaryngologist and consist of conventional immunosuppressive therapy, biologic agents and endoscopic manipulations.

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Immunopathology of active and remitting granulomatosis with polyangiitis (Wegener’s)

L. Rani, R. Minz, A. Sharma, S. Anand, D. Gupta, N. Panda, V. Sahuja
PGIMER, Chandigarh, India

Introduction.– Granulomatosis with polyangiitis (GPA) is a complex relapsing and remitting autoimmune vasculitis. Immune system aberrations have not been completely described in this disease. We compared T-cell activation status, expression of co-stimulatory molecules, T-regulatory cells (Tregs), cytokine profile and FOXP3 & ROR-γt gene expression in peripheral blood mononuclear cells in active as well as in remitting GPA.

Methods.– Total 21 cases of GPA fulfilling ACR and CHCC criteria in active state as well as in remission state (6 months post therapy) and 20 healthy controls were enrolled in the study. PBMCs were isolated and expression of activation markers (CD25 & CD69), co-stimulatory molecules (CD152 & CD28), Tregs (CD4+CD25+FOXP3+) were analysed by flow cytometry. Th1/Th2 and Th17 cytokines were detected in culture supernatants after 24 hr stimulation with PR3 antigen. Serum IL-17 and IL-8 were studied by ELISA. Gene expression profiles of FOXP3 and ROR-γt in peripheral blood was analyzed by Real Time PCR.

Results.– We have defined the Immunopathology of active and remitting as shown in the table below (table I). There was also increased IL-17, IFN-γ and TNF-α secretion in culture supernatants in remission as compared to healthy controls.

Discussion.– T-cells remain in an activated state even during remission. Remission is achieved by up-regulation of CD152 molecules probably in Tregs and also on CD8+ cells. There is also increase in Tregs during remission. The increased levels of IL-17 in active disease indicate the scope of anti IL-17 therapy. Our finding of increased ability to secrete IL17, TNF-α, IFN-γ during remission, suggests that these are effector
Table I

<table>
<thead>
<tr>
<th>Immunopathology of active vs. remitting GPA</th>
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</thead>
<tbody>
<tr>
<td>Active GPA</td>
</tr>
<tr>
<td>CD3⁺</td>
</tr>
<tr>
<td>CD3⁺CD25⁺</td>
</tr>
<tr>
<td>CD4⁺CD25⁺FOXP3⁺</td>
</tr>
<tr>
<td>FOXP3 gene expression</td>
</tr>
<tr>
<td>ROR-γt</td>
</tr>
<tr>
<td>c-c-IL-17 &amp; s-IL-17A</td>
</tr>
<tr>
<td>c-TNFα, IL-6 &amp; IL-10</td>
</tr>
</tbody>
</table>

a = culture supernatants after PR3 stimulation.
b = serum.

memory cells and they should be targeted and eliminated, to prevent relapse. Also modulating CD152 molecule in Tregs can also prevent relapse.

Conclusion.– To achieve relapse free remission, there is need to give:
- Anti-IL-17;
- by eliminating PR3 specific effector memory cells;
- by modulating CD152.

Further readings

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P77
**Tracheobronchial stenoses (TBS) in granulomatosis with polyangiitis (Wegener) (GPA)**
C. Girard¹, V. Cottin¹, J.-F. Cordier¹, L. Guillevin²
1. Hospices civils, Lyon, France
2. AP-HP, hôpital Cochin, Paris, France

Introduction.– TBS, severe manifestations of GPA, sometimes respond poorly to corticosteroids (CS) and cytotoxic drugs.

Methods.– We describe 19 GPA patients with ≥1 subglottic (SGS) or bronchial stenoses (BS) treated in two medical departments (Paris and Lyon). Their clinical, biological, radiological and therapeutic data were collected and analyzed, with comparisons between SGS and BS patients.

Results.– Among the 19 patients (13 women, 6 men) included, 7 had BS and 12 SGS. Their median age at GPA onset was 29 years. All but two were ANCA+ (15 anti-PR3+, 2 anti-MPO+). Histology of the 11 tracheobronchial biopsies obtained found no evidence of GPA. TBS outcome was independent of the GPA course. Despite conventional therapy, SGS patients frequently relapsed (1–8 times). Notably, cyclophosphamide (CYC) was never effective against SGS but seemed to prevent relapses.

Discussion.– Our findings confirmed that TBS are unusual GPA manifestations. In this context, patients were younger and mostly female, had non-specific histology. TBS outcomes were independent of other visceral involvement(s) and conventional drugs seemed to be ineffective, especially against SGS, although CYC might help control BS. Local treatments, combined with classical medical management of GPA as warranted, are being recommended more-and-more frequently. In particular, local CS injection combined with mechanical dilation has been useful in treating SGS. Prospective studies are needed to optimize local and medical TBS therapy, and determine the real value of other immunosuppressants, especially rituximab.

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P78
**Wegener or Churg Strauss**
S. Saliba
Centre hospitalier intercommunal Poissy-Saint-Germain-en-Laye, service de néphrologie–hémodialyse, Poissy, France

Introduction.– Systemic vasculitis is a rare autoimmune disease that causes the blood vessels to become inflamed. There are many types. We present a case of a 38-year-old woman who developed multiple symptoms of systemic necrotizing vasculitides.

Methods.– Patient A., 38-year-old, was hospitalized many times from February 2012 for dyspnea, wheezing and dry cough considered as an asthma triggered by chronic rhinosinusitis with nasosinal polyposis with favorable evolution under corticotherapy. Renal function was normal. In November, patient presents aggravation of dyspnea with apparition of lower limb edema, polyarthritis, chest pain on inspiration, diarrhea and epistaxis. Creatinin: 639 μmol/L; proteinuria: 8 g/24 h; hematuria: 880/mm³. Inflammatory syndrome; and hypereosinophilia 4500 (41%).

Immunologic exams finds P-ANCA anti-MPO and the renal biopsy mark lesions of angitis:
- fibrinoid necrosis;
- extracapillary proliferation of pseudo-crescents;
- massive infiltration by polymorphonuclear neutrophils, plasmocytes and macrophages. NO eosiinophils;
- neutrophil granulomas.

Chest scan: mediastelial nodules and pulmonary parenchymal granulomas. Pericardial effusion.

We started a treatment by extrarenal epuration three times weekly, therapeutic plasma exchange and three bolus of solumedrol 1 g each and then, then changed to oral corticotherapy. Two courses of cyclophosphamide was complicated by sepsis. No recovery of renal function.

Results.– We are faced with interesting case of necrotizing vasculitis with P-ANCA anti-MPO+ with multiple organ damage including kidney. Clinical elements can evoke syndrome Churg Strauss, but the histology guide us to necrotizing granulomatosis frequently compatible with Wegener syndrome.

Conclusion.– Push further investigations in the case of adult-onset asthma may reveal unexpected pathology. A clear differentiation between Churg Strauss and Wegener syndromes is not clear in some cases. Wishing that you add this case to your database through reference centers.

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