Maintenance treatment in childhood granulomatosis with polyangiitis

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Introduction.— Granulomatosis with polyangiitis (GPA) is a rare but potentially life or organ threatening disease. The majority of children present with pulmonary bleeds and/or renal failure. Most treatment regimens are derived from the adult literature, and no studies have been performed in pediatric patients. The aim of this study is to describe the outcome of maintenance treatments in a large group of children with GPA.

Patients.— All consecutive children diagnosed with GPA since January 2000 at the Hospital for Sick Children, Toronto, were included. Demographic data, and clinical and laboratory data at diagnosis and follow-up were collected. Descriptive statistics were used for these preliminary results.

Results.— Thirty-two children were included; 21 girls and 11 boys, median age of 13.7 years at diagnosis. Anti-neutrophil cytoplasmic antibody (ANCA) was positive in 30 children [26 c-ANCA with 25 anti-proteinase-3 (anti-PR3), four p-ANCA with four anti Myeloperoxidase (anti-MPO)] and two were ANCA negative (one anti-PR3 positive). Eight children had limited disease and 24 systemic diseases. Induction therapy in the systemic patients consisted of pulses of cyclophosphamide i.v. (mean 7 pulses) and methylprednisone (mean 5 pulses) i.v., six children received plasmapheresis. Maintenance treatment in this group consisted of methotrexate (MTX) in seven, azathioprine (AZA) in 14, and mycophenolate mofetil (MMF) in three children. In the limited disease group, treatment consisted of oral prednisone in all, MTX in seven children and AZA in one as initial treatment. Relapses were seen in 14 children. Fifty percent of relapses (n = 7) were within the first 12 months of disease. Of the 14 patients, two children with limited disease relapsed, both while still on MTX. Eleven children with systemic disease relapsed on treatment; four on MTX, five on AZA and two on MMF.

Conclusion.— Relapses are frequent (22% in first year of treatment) in childhood GPA despite inductions and maintenance treatment. Relapses are higher in children with systemic GPA (50%) compared to limited GPA (25%).

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GPA and MPA patients have different serum cytokine profiles

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Introduction.— The ANCA associated vasculitis (AAV) subsets – granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) are often regarded and treated as one diagnostic group, but recent genetic data demonstrate that they are not. Here we studied GPA and MPA serum comparing a set of cytokines implicated in AAV.

Patients.— Peripheral blood were collected from 39 active AAV patients at baseline and following 6 months of therapy. Thirteen age- and sex-matched healthy individuals were used as controls.

Twenty-six out of thirty-nine patients had a GPA diagnosis (24 PR3+ / 2 MPO+) and 13 had MPA (all MPO+). Disease activity was estimated by Birmingham Vasculitis Activity Score 2003 (BVAS) and CRP. Serum samples was analyzed for the presence of IL-6, IL-8, IL-10 and IL-17A by cytomteric bead array.

Results.— The AAV patients displayed significantly elevated levels of IL-6 and IL-10 as compared to age-matched healthy controls but not of IL-8 and IL-17A.

Next, the samples were subgrouped according to diagnosis and auto-antibody profile. The GPA group had higher baseline of both IL-6 and IL-17 than MPA, although only few patients had detectable IL-17 (all GPA, 6PR3/1MPO). In the GPA samples, but not in MPA, the levels of IL-6, -8 and -17 decreased significantly at follow-up, and IL-10 showed a trend towards decrease. These differences were even more pronounced when comparing PR3+ vs. MPO+.

Conclusion.— GPA and MPA have overlapping disease manifestations and are treated similarly. Still, recent data suggest that the genetic make-up is distinct between the two. Hence the underlying immune responses could have different causes.

In contrast to recent publications, our data does not support the notion of IL-17 being generally increased in AAV patients. Instead we found that GPA/PR3 patients down regulated the studied cytokines after initiated therapy much more robustly than MPA/MPO. These data indicate that GPA and MPA, or actually PR3+ and MPO+, could be immunologically distinct and hence require differences in treatment approach.

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A case of lung biopsy-proven MPO-ANCA positive granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis)

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Introduction.— We report a rare case of MPO-ANCA positive GPA with typical pathological findings in the lung nodule which was obtained by open biopsy. We also discuss the characteristic of MPO-ANCA positive GPA often seen in Asian countries, with other cases we have experienced in our hospital.

Patients.— A 61-year-old man suffered from intractable secretory otitis media in his right ear in March 2012. Two months later, he complained of general fatigue and body weight loss. Five month later he suffered from scleritis and intermittent fever, then he visited a doctor in November 2012. Mass lesions were found in his both lungs by chest radiography and positron emission tomography-computed tomography (PET-CT).

He was referred to the department of respiratory medicine of our hospital. The CT revealed mass shadow in both lungs and sinusitis. Open lung biopsy was performed. The specimen, obtained from the left lower lobe, showed granuloma with multinucleated giant cells and
necrotizing vasculitis without eosinophils. The patient was seronegative for PR3-ANCA and seropositive for MPO-ANCA. However, he had no history of bronchial asthma or eosinophilia. He was diagnosed with MPO-ANCA positive GPA according to the American College of Rheumatology classification criteria. He developed an acute renal failure after he admitted our hospital, then he was treated with intravenous methylprednisolone pulse therapy, and following oral prednisolone (50 mg/day), and intravenous cyclophosphamide pulse therapy.

Results.— We analyzed 30 GPA patients who visited our hospital. Characteristics of MPO-ANCA positive GPA were a little different from PR3-ANCA positive GPA. There was a tendency that kidney involvement preceded pulmonary or upper airway involvement in MPO-ANCA positive GPA.

Discussion.— It is rare for histological findings of MPO-ANCA positive GPA to show typical granuloma with multinucleated giant cells. We thought that the patient is an important case to consider the pathogenesis of MPO-ANCA positive GPA.

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Interleukin 15, CD56+ T-cells and ANCA-associated vasculitis (AAV)
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Introduction.— Interleukin-15 (IL-15) is a proinflammatory cytokine that is overexpressed in AAV and is linked to the expansion of CD4+ effector memory T-cells (TEM). In AAV in remission a persistent expansion of these CD4+ effector memory T-cells has been observed. It is hypothesized that IL-15 is able to up regulate the expression of NK cell receptors, e.g. NKG2D and CD56. These molecules seem to be involved in tissue injury as they activate cells via interaction with MHC class I related molecule A (MICA) or CD56 ligand respectively. NKG2D and CD56 are also expressed on a unique sub-population of effector CD4+ cells (CD56 (+) CD4+ T-cells) capable of mediating TCR-independent immune activation. In the present study we assessed the expression of NKG2D and CD56 on CD4+ T-cells of AAV and if expression of these molecules was influenced by IL-15.

Methods.— The distribution of CD4+ TEM and the proportion of CD56 + CD4+ T-cells and NKGD2+ CD4+ T-cells were analysed in 45 AAV-patients and 30 HC’s by FACS. In vitro effects of IL-15 on the expansion of CD4+ TEM and up regulation of surface cytotoxic markers were assessed in the same way.

Results.— We observed an increased proportion of circulating CD4+CD56+ T-cells in AAV as well as NKGD2+ CD4+ T-cells in patients in remission compared to HC (13.6 vs. 0.6 P < 0.0001 and 14 vs. 0.7 P < 0.0001). 80% to 90% of these cells were CD4+ effector memory T-cells. The percentages of the CD56+ CD4+ T-cells and NKGD2+ CD4+ T-cells were constant over time. We found a significant positive correlation between the percentages of CD56+ CD4+ T-cells and age in GPA patients in remission (r = 0.6 P = 0.004). Stimulation of PBMCs with IL-15 increased not only the proportion of CD4+ memory cells (CD45RO+) but also the expression of CD56 and NKGD2 on these cells.

Conclusion.— Increased IL-15 expression is likely the driving force behind the persistent expansion of cytotoxic CD4+ effector memory T-cells in AAV.

Further readings


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Resolution of proteinuria and hematuria in ANCA-associated nephritis
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Introduction.— Proteinuria and hematuria are hallmarks of renal involvement in ANCA-associated vasculitis (AAV). Their disappearance is considered an indication of response to therapy, however, little is known of about when this could be expected and the clinical significance if they remain positive.

Patients.— Follow-up data from 28 patients with AAV and nephritis treated with cyclophosphamide, were collected retrospectively. Proteinuria and hematuria was defined as > +1 on dipstick testing. Duration was calculated using Kaplan-Meier plots and patients were censored at death or start of dialysis.

Results.— Median age at diagnosis was 68.3 years (IQR 53.4–73.1) and median p-creatinine 240 microm/L (IQR 113–406). MPO-ANCA was detected in 17 patients and PR3-ANCA in 12. At diagnosis 1 patient did not have hematuria and seven did not have proteinuria. The median time to resolution of hematuria was 104 days (IQR 76–364) and for proteinuria 238 days (76–1213).

Duration of proteinuria and hematuria was not correlated to each other (r = −0.07), to age or to initial p-creatinine, but duration of proteinuria was related to initial U-albumine (r = 0.60). Resolution was faster in PR3-ANCA positive patients compared to MPO-ANCA (hematuria: 76 vs. 127 days, P = 0.01; proteinuria 92 vs. 843 days, P = 0.036).

At 3 months nine patients had no hematuria, none of these developed end-stage renal disease during follow-up, while five out of 18 patients with persistent hematuria experienced such event (P = 0.13).

Conclusion.— There are huge variations in the time it takes for proteinuria and hematuria to disappear in AAV-nephritis after start of treatment, but duration of hematuria is usually shorter than duration of proteinuria. Duration of both signs is shorter in PR3-ANCA associated disease.

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