
Case Report

Central Nervous System Involvement under Intensive Immunosuppressive Treatment in a Patient Diagnosed with Granulomatosis Polyangiitis: A Case Report

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Abstract

Granulomatosis polyangiitis (Wegener's granulomatosis) is an ANCA-associated necrotizing vasculitis. The disease involves upper respiratory tract, the lungs and kidneys but central nervous system (CNS) involvement is 1-5%.

A 40-year-old male patient was admitted to the hospital with joint pain, rash, aphthous lesions. The skin biopsy from the lesion showed leukocytoclastic vasculitis. The patient had c-ANCA positive and was diagnosed granulomatosis polyangiitis. He was treated with a pulse steroid and cyclophosphamide. Before the 5th session of therapy, the patient developed hemoptysis and hematuria. Thorax CT (computerized tomography) showed a diffuse alveolar hemorrhage and hence plasmapheresis and IVIG (intravenous immunoglobulin) were added to the treatment. Two days after IVIG, the patient developed globe vesical, headache and respiratory arrest. MR (magnetic resonance) showed CNS involvement. The patient was treated with a pulse steroid, but did not respond to therapy and died after 5 months since establishing the diagnosis.

More studies are needed to identify effective treatment and course of disease for patients with central nervous system involvement.

Key words: alveolar hemorrhage, central nervous system involvement, granulomatosis polyangiitis, immunosuppressive treatment, renal failure

Introduction

Granulomatosis Polyangiitis (GPA) is an ANCA-associated necrotizing vasculitis and affects small and medium-sized vessels. ANCA is positive in 82-90% of patients [1]. The disease involves upper respiratory tract, lungs and kidneys and can affect people of any age, but is more common in the 5th and 6th decade [2] Patients may

be present with constitutional symptoms like fever, arthralgia, weakness or with nose bleeding, sinusitis, hematuria, hemoptysis, shortness of breath or acute renal failure. Skin involvement is seen in approximately 50% of patients, upper respiratory tract involvement in 90% and renal involvement in 20% at the beginning but at follow-up in up to 80% [2,3].

The disease affects peripheral nervous system in 50-60% of patients, but central nervous system (CNS) involvement is 1-5%. Peripheral nervous system involvement occurs as peripheral neuropathy (mononeuritis multiplex or polyneuropathy) or cranial nerve neuropathies. Involvement of the central nervous system occurs as cerebral vasculitis or involvement of meninges [4-6].

In our case, the patient was admitted to the hospital with constitutional symptoms and at the follow-up the kidneys and the lungs were affected and central nervous system involvement occurred as well.

Case report

A 40-year-old male was admitted to our hospital with joint pain, rash, aphthous lesions and hemorrhagic crusts at nasal septum following a 2 week antibiotic course for ear infection. Skin biopsy showed leukocytoclastic vasculitis with negative immunohistochemistry, and nasal septum biopsy was non-specific. His baseline creatinine level was 0.79 mg/dl and 24-hour urine protein was 1 g/day. C-ANCA was positive, anti-PR3 level was 2.4 U/mL, thorax CT did not show any lung involvement. We could not perform a kidney biopsy, because the patient was using enoxaparine for treatment of deep venous thrombosis in vena saphena magna. Serum protein electrophoresis was normal, physical examination revealed no lymphadenopathy, ANA was negative. The patient was diagnosed with GPA and treatment with a pulse steroid (1 g/day, three days) and cyclophosphamide (500 mg/m²/day, one day) was initiated. Three weeks later (before the

2nd session of treatment) the patient was admitted to the hospital with joint pain; creatinine levels were 5.4 mg/dl and anti-proteinase 3 level was 55 U/mL. We suggested performing a kidney biopsy, but the patient refused. Four sessions of plasma exchange were performed and methylprednisolone dose increased to 1 mg/kg/day and therapy with cyclophosphamide was continued.

After treatment creatinine levels decreased to 2 mg/dl. The steroid dose tapered to 32 mg/day and before the 5th session of the pulse therapy the patient developed hemoptysis and hematuria. Thorax CT showed diffuse alveolar hemorrhage and anti-PR3 level was 59 U/mL. Sputum acid-fast bacillus was negative. We continued pulse therapy with 500 mg/day (3 days) methylprednisolone and 8 sessions of plasma exchange were performed. The patient was treated with 2 g/kg intravenous immunoglobulin (IVIG). There was no adverse event attributed to IVIG treatment. Patient's urine output decreased and he required hemodialysis. After treatment, arterial

blood gas showed no hypoxia and he did not require chronic hemodialysis. However, he developed thrombocytopenia and therefore cyclophosphamide therapy was stopped and for maintenance therapy mycophenolate mofetil was initiated. After the 2nd session of IVIG treatment the patient complained on weakness in his lower extremities and urinary retention. The neurological examination revealed flask paraplegia. He suddenly developed headache, loss of consciousness and respiratory arrest. He was transferred to Intensive care unit. Cranial CT showed intraventricular hemorrhage and hydrocephalus. MR showed dural soft tissue masses, wrapping around the spinal cord at the cervical and thoracic levels consistent with disease activity (Figure 1). The patient was treated with 500 mg/day (3 days) methylprednisolone, but he did not respond to this therapy. The patient passed away after 5 months of establishing the diagnosis. There was no response to treatment.

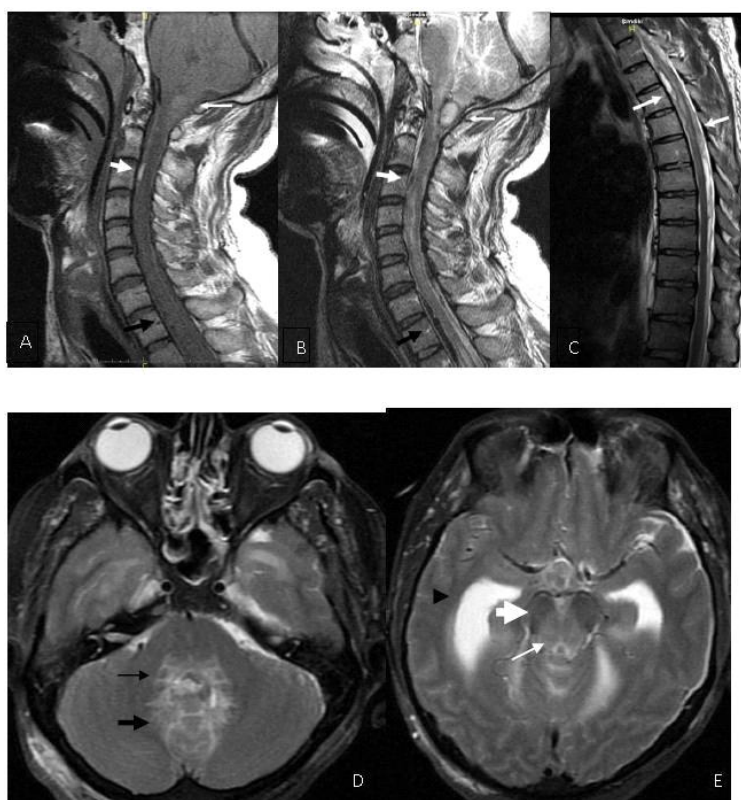


Fig. 1. MR images show dural soft tissue masses, wrapping around the spinal cord at the cervical and thoracic levels. A. Sagittal T1 weighted MR image (cervical level), B. Sagittal T1 weighted MR image (thoracic level), C. Sagittal T2 weighted MR image (thoracic level), D. Axial T2 weighted MR image (pons level), E. Axial T2 weighted MR image (mesencephalon level). Spinal cord is hyperintense at the cervical and upper thoracic level. Dural masses are hyperintense on T1-weighted images and hypo- and hyperintense on T2-weighted images depending on the stage of the hemorrhage (white and black arrows). There is a hematoma at the craniocervical junction with minimal cord compression (white thin arrow). Symmetrical hyperintensity of the midbrain (thick white arrow), pons (black arrow), periaqueductal gray matter (white arrow) and cerebellum (thick black arrow) is well seen on the T2 weighted scan, these findings are compatible with brainstem involvement. Hydrocephalus is present (arrowhead).

Discussion

We presented a case of a patient diagnosed with granulomatosis polyangiitis and during the course of the di-

sease he developed CNS involvement in spite of the aggressive treatment. CNS involvement is a rare finding in the course of a disease, but in our case leptomeningeal

and cerebral vasculitis appeared concomitantly and led to death of the patient.

CNS involvement in granulomatosis polyangiitis is thought to be caused by three different mechanisms. The first mechanism is the vasculitic involvement of the small-medium sized vessels of the brain and spinal cord. The second mechanism is spread from the upper respiratory lesions to the central nervous system by bone and cartilage destruction. The third mechanism is arising from granulomatous lesions in the brain and meninges [7-9]. Cerebral involvement usually occurs with progression of the disease, but sometimes it may occur as the first manifestation of the disease. Many cases with primary CNS lesions respond well to immunosuppressive therapy and full recovery is possible [10-14]. There are some cases successfully treated with rituximab, but the data is limited [15]. Cerebral vasculitis is the most common form of central nervous system involvement as it was in our case and it may occur as intracerebral or subarachnoid hemorrhage or transient ischemic attack, ischemic infarct of brain and spinal cord, or as arterial-venous thrombosis [8,13]. It may present with neurological findings such as epileptic seizures, loss of consciousness, or neuro-psychiatric symptoms such as behavioral disorders [7,8]. Chronic hypertrophic pachymeningitis is a more common form of leptomeningeal involvement and is usually seen in localized disease [14,16]. Our case showed features of cerebral involvement. The hemorrhage was thought to be related to the vasculitic involvement of the brain tissue, and there was also a spinal cord involvement. Platelet count was below normal, but enough to prevent spontaneous hemorrhage and there was no detectable coagulation abnormality. Treatment resistance was defined as unchanged or increased disease activity in ANCA-associated vasculitis after 4 weeks of treatment with standard therapy or a reduction of <50% in the disease activity score after 6 weeks [17]. Therefore, this case can be regarded as treatment resistant. There is no consensus about treatment of severe relapsing or treatment of resistant ANCA-associated vasculitis. There is no consensus about effective treatment and there is no study about the course of the disease and mortality in Wegener granulomatosis with neurological involvement. In clinical practice a high dose of steroid and cyclophosphamide seems to be effective to induce remission.

Conclusions

In conclusion, in addition to standard therapy in our case we used IVIG and plasmapheresis, but the course of disease was fatal. More studies are needed regarding treatment in generalized disease with neurological involvement.

Conflict of interest statement. None declared.

References

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