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Case Report

Microscopic Polyangiitis Presenting as Pyrexia of Unknown Origin with Neurological Symptoms and a Management Dilemma

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Abstract

We present case of Microscopic Polyangiitis, diagnosed in a 63-year-old female who developed neurological symptoms and hematological abnormalities prior to typical renal involvement. Extensive sepsis and other workups remained unrevealing in identifying cause of persistent fevers, leukocytosis and thrombocytosis except that p-ANCA and MPO were positive. Definitive diagnosis was delayed because of interim sepsis from pneumonia and UTI with MDR organisms. The patient failed antibiotics treatment and developed progressive acute kidney injury. Later, kidney biopsy confirmed the diagnosis and patient was started on immunosuppressant therapy with good clinical response. Timely diagnosis and management of vasculitis is paramount to improve prognosis. **Background:** Microscopic Polyangiitis (MPA) belongs to family of antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitides that also includes granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis [1]. Originally termed as "microscopic form of periarteritis nodosa" by Friedrich Wohlwill, was later renamed, 'microscopic polyangiitis' in 1994 through the Chapel Hill Consensus Conference. MPA is an idiopathic systemic vasculitis characterized by immune mediated necrotizing inflammation of small to medium sized blood vessels and presence of circulating ANCA. MPA has a reported incidence of 2.7 to 94 per million with slight male predominance and average age of onset between 50-60 years [2-5]. **Objectives:** Although, introduction of aggressive immunomodulatory therapy has improved MPA prognosis, it remains grave in untreated cases. Sepsis could complicate the clinical picture but timely diagnosis and management are important to improve prognosis. Excessive use of broad-spectrum antibiotics in fever of unknown origin cases management should be avoid to limit developing antibiotic resistance.

Case Presentation

We present case of a 63-year-old Hispanic female, non-smoker and non-drinker with past medical history of hypertension who initially presented to the Emergency Department (ED) with complaint of bilateral posterior neck pain. Patient denied preceding head trauma or fall. Clinical exam, including neurological exam was unremarkable. Initial laboratory workup showed normocytic hypochromic anemia, elevated platelets, lymphocytes and monocytes. Initial non-contrast head CT-scan (NCHCT) showed chronic left subdural hematoma with mass effect and slight midline shift (Figure 1). Patient's symptoms improved after hematoma evacuation and hematological abnormalities self-resolved prior to discharge. Later, Dural biopsy was suggestive of chronic severe inflammation with abundant plasma cells. Two months later from her initial presentation, patient developed sudden onset of right sided fascial drop with an initial National Institutes of Health Stroke Scale (NIHSS) score of two. Repeat NCHCT showed acute versus subacute infract in the left corona radiata extending to the basal ganglia (Figure 2). CT-angiogram showed a 3mm aneurysm at the internal carotid artery terminus and a 2mm aneurysm at the left middle cerebral artery bifurcation. During the hospital course, neurological deficit self-resolved with NIHSS score of zero, but patient developed persistent fevers that prompted further evaluation. Repeat laboratory assessment

revealed baseline normocytic hypochromic anemia with interval leukocytosis and thrombocytosis. Peripheral blood smear showed neutrophilia and no blast cells. Sepsis workup including chest X-ray (CXR), urine analysis, covid-19 PCR, HBV/HVC/HIV screenings, Urine *Legionella* antigen, tick-borne antibodies panel, blood parasites, tuberculosis and syphilis screens, blood bacterial and fungal cultures, were sent and all came back negative. PAN-CT scans were also unrevealing. Furthermore, myeloproliferative disorders work up including JAK2, BCR-ABL and MPL were negative. The echocardiogram did not visualize any vegetations. At this point, autoimmune panel was sent that revealed elevated C-reactive protein and erythrocyte sedimentation rate, positive p-ANCA with titer of 1:320, positive myeloperoxidase antibodies (MPO) and negative anti-neutrophilic antibodies (ANA). Self-resolution of fevers over few days without empiric antibiotics use was suggestive of autoimmune origin of fever. In-house rheumatology service was consulted and recommended further evaluation on outpatient follow up. Patient was discharged to a short-term rehabilitation facility with clinic appointment.

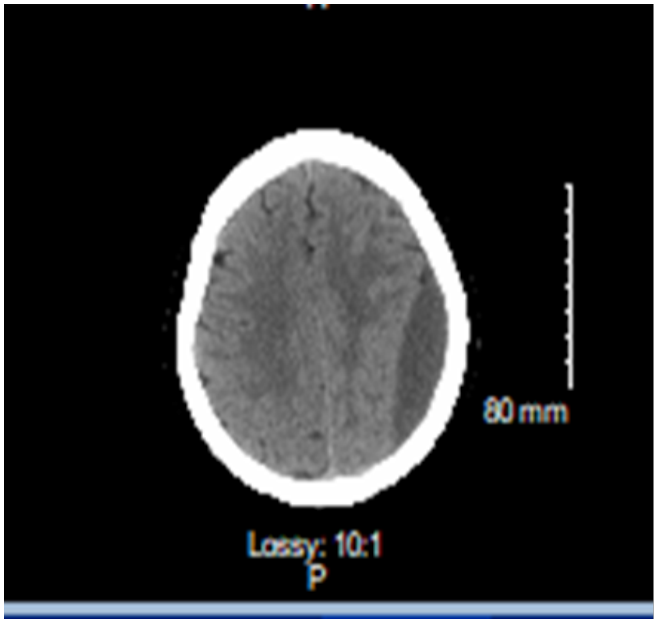

Figure 1: First NCHCHT (Non-Contrast Head Computerized Tomography) Scan showing chronic left subdural hematoma.

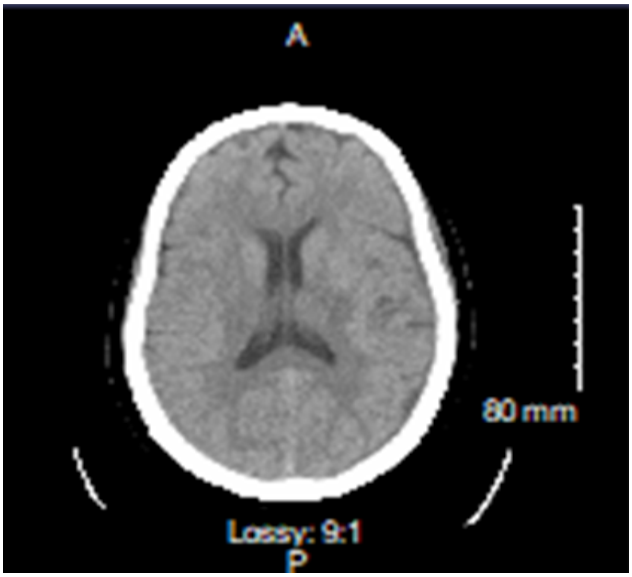

Figure 2: Repeat NCHCT (Non-Contrast Head Computerized Tomography) Scan showing subacute infarct in left corona radiata.

During her stay at rehabilitation facility, patient spiked fevers again and developed acute hypoxemic respiratory failure secondary to hospital-acquired pneumonia. Repeat CXR showed right lower lobe infiltrates. Patient was transferred to medical service and treated with supplemental oxygen and broad-spectrum antibiotics i.e., piperacillin/tazobactam, vancomycin and azithromycin; later vancomycin and azithromycin were discontinued when culture for *Staphylococcal Aureus* and Urine *Legionella* antigen were negative respectively. Piperacillin/tazobactam was continued for 10 days. Patient improved clinically but two weeks later from this event, she spiked fevers again and became septic from urinary tract infection which grew multi-drug resistant gram-negative rods (*Escherichia coli* and *Klebsiella*). Patient received antibiotics as per urine culture sensitivities reports. Although, repeat urine cultures became negative but patient remained febrile and had persistent leukocytosis. Infectious disease (ID) service was consulted who recommended treatment with meropenem for 14 days if white cell counts lowered significantly; otherwise, to stop after five days. Meropenem was stopped at day 5 because of lack of response. Whole-body indium single photon emission computerized tomography (SPECT) scan was done at this point

and was negative for occult infection. All antibiotics were stopped considering central cause of fever and patient was observed clinically.

Over the course, patient developed new neurological deficits including right lower extremity weakness with right foot drop and bilateral lower extremities paresthesia's. MRI lumbar spine revealed multiple levels of degenerative changes with mild to moderate lumbar spinal stenosis. MRI brain was only suggestive of evolution of prior infract (Figure 3). Lower extremities DVT study was negative. Repeat laboratory assessment was consistent with persistent leukocytosis and thrombocytosis, positive p-ANCA with titer 1:640 (doubled from prior levels), positive MPO levels of 106.3 and interval development of rapidly progressive acute kidney injury. Considering, multi-systems involvement and rapidly declining kidney functions, left kidney biopsy was performed for definitive diagnosis and patient was transferred back to our institution for further management.

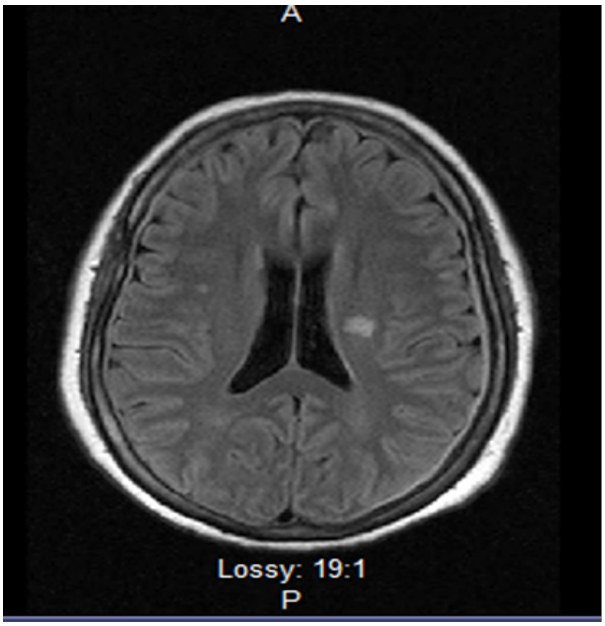

Figure 3: MRI (Magnetic Resonance Imaging) Brain without contrast showing old infract in the left corona radiata.

On assessment, patient was found profoundly deconditioned from her baseline and had become bed-bound because of right leg weakness and worsening neuropathic pains. Demyelinating sensorimotor axonal neuropathy was found on electromyography. We followed-up with biopsy report, which was consistent with focal segmental/crescentic glomerulonephritis of pauci-immune type (Figure 4). Thus, a diagnosis of MPA was confirmed. Case was discussed with multi-disciplinary teams (ID, Neurology and Rheumatology) and decision was made to start patient on remission induction therapy with pulse dose steroids and cyclophosphamide, after all cultures returned negative and patient remained afebrile. Patient tolerated the therapy well with good clinical response. Improvement of leukocytosis, thrombocytosis and renal functions were noted after first cycle of induction therapy. In-patient physical rehabilitation was continued.

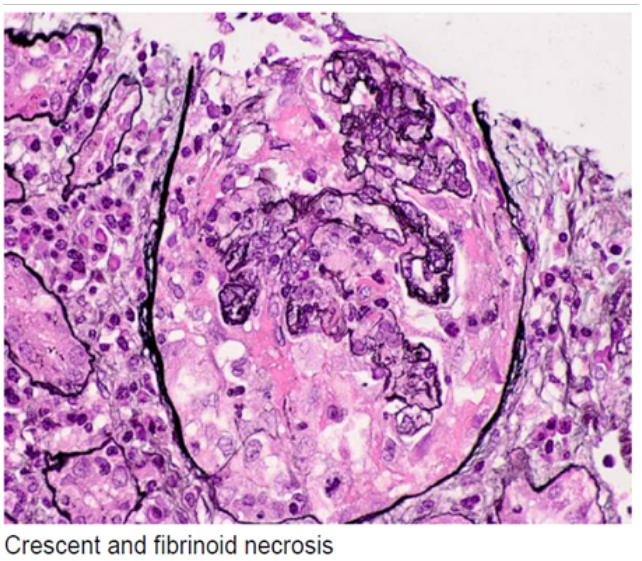

Figure 4: Left Kidney biopsy showing crescent and fibrinoid necrosis. H&E (Hematoxylin & Eosin) Stain.

Post-induction therapy, patient was discharged to a short-term acute rehabilitation facility. Steroids were rapidly tapered off due to steroid-induced psychosis and remission maintenance therapy was continued with cyclophosphamide. Hematological abnormalities and acute kidney injury have resolved. MPO levels are negative now. Patient has returned to her baseline. She is doing clinically well on maintenance therapy and has regular follow-ups with rheumatology service.

Discussion

In presented case, patient had an atypical disease course i.e., first developed central neurological symptoms; followed by unexplained fevers, persistent leukocytosis and thrombocytosis; later developed peripheral neuropathies and rapidly progressive glomerulonephritis causing acute renal failure. This is contrary to typical MPA presentation where kidneys and lungs are usually the first and most commonly affected organs. Furthermore, interim sepsis from pneumonia and UTI complicated the clinical picture and added to delay in definitive diagnosis. Neurological involvement in MPA is common and has been observed in 37-72% of patients [6,7]. Peripheral manifestations occur more frequently than central ones, typically present as mononeuritis multiplex or symmetrical polyneuropathy that can be progressive if untreated. Central involvement has been observed in only 17% of cases and

ranges from patchy meningitis to cerebral hemorrhage or infarction [8,9].

In our case, patient achieved remission after induction therapy with corticosteroids and immunomodulatory therapy i.e., cyclophosphamide that is a first line agent, and combined with steroids, is standard of care for severe active disease as per American College of Rheumatology and Vasculitis Foundation guidelines 2021. Treatment of relapse is same as that of remission induction. ANCA levels can be used to assess disease activity, however, do not always correlate well. The reappearance of MPO antibodies have been shown to be more suggestive of disease relapse [10].

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