Possible central nervous system vasculitis as an early presentation of Crohn's disease.
A challenge in diagnosis and management

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The vasculitides are a group of disorders that affect vessels of varying size, type, and location. They are characterized by the presence of leukocytes in the vessel wall, with resultant damage to mural structures.[1] Angiitis in the central nervous system (CNS) may be due to primary or secondary involvement of the CNS by systemic disorders, including an infection, systemic vasculitis, or a connective tissue disease.

Crohn's disease (CD) is a type of inflammatory bowel disease that primarily affects the gastrointestinal tract, but it may also affect other organ systems. Although vasculitis and arthritis have been reported as the initial manifestations of CD,[2] CNS vasculitis as a presenting symptom of CD is exceptional. In this report we describe the case of a male patient with CD, which manifested initially as CNS vasculitis.

A 44-year-old male presented to the emergency room with a 2-day history of severe abdominal pain that was vague, progressive, and diffuse without radiation. It was associated with copious, watery diarrhea without mucus or blood. There was no tenesmus, nausea, or vomiting. The patient had a band-like headache with a decreased level of consciousness (Glasgow Coma Scale 13/15),[3] but no photophobia, blurred vision, new weakness, or abnormal sensation. He had no convulsions or fever. The patient had a 5-year history of untreated hypertension. Three months previously, he had suffered an ischemic stroke that resulted in left hemiaplasia (power 0/5). At the time of presentation, he was taking prophylactic aspirin (Bayer, Leverkusen, Germany). On examination, the patient was hypertensive (blood pressure 200/128 mm Hg) with a heart rate of 100 beats per minute. A non-itching palpable petechial rash was distributed over the lower limbs and buttocks. There was no lymphadenopathy, or lower limb edema. His abdomen was distended, with diffuse abdominal tenderness, hyperresonance to percussion, positive bowel sounds, and no organomegaly. There was no neck rigidity or signs of meningitis. His right side was normal, while the left upper and lower limbs had 0/5 power with hypertonia and hyperreflexia. His chest examination was normal.

A provisional diagnosis was made of Henoch-Schonlein purpura or another vasculitis, meningitis, or intestinal ischemia. Laboratory investigations showed the following: hemoglobin - 17 g/dL (reference range: 13-16), white blood cells - 17.6×103/μL (reference range: 4.5-11), platelets - 387×103/μL (reference range: 150-350), neutrophils - 86.9%, and D-dimer - 14.7μg/mL (reference range: <0.5). Renal profile, liver function tests, and cerebrospinal fluid profiles were within normal limits. Total bilirubin was 37 mg/dL (reference range: 3-17), and direct bilirubin was 6 mg/dL (reference range: 0.1-0.3). Urine analysis showed trace amounts of blood, with no protein, and no casts. An abdominal CT scan showed mild thickness in the ileal and ileocecal wall, without other signs of intestinal ischemia. A brain CT scan showed small hypodense areas at the right corona radiata, anterior limb of the internal capsule, and left internal and external capsule resulting in a suspected diagnosis of CNS vasculitis. Histopathology of a skin biopsy from the left thigh revealed peripheral vasculitis.

The patient was admitted and his condition deteriorated the following day. He became tachypnic with respiratory distress, hypotensive, and somnolent. He was started on dopamine (Hospira Inc, Lake Forest, IL, USA) to support blood pressure, and elective intubation was performed. He was transferred to the intensive care unit for further management, where he developed coffee ground hematemesis. A large volume of blood was aspirated through a nasogastric tube. Two units of blood were transfused. An urgent endoscopy was performed; it showed large ulcers with vessels in the center, Dieulafoy's lesions, severe esophagitis, and duodenitis. Three hemoclips (Weck Closure Systems, NC, USA) were applied to control the bleeding. The patient became hemodynamically stable and dopamine was stopped. Subsequently, he developed melena, and on colonoscopy was found to have multiple ulcers in a skip pattern involving the colon. Biopsy tissue taken from the ileocecal valve area showed granulation tissue formation with a pattern of distribution consistent with CD. Considering the possibility of vasculitis secondary to CD, we requested all vasculitis investigations. Urine

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analysis showed +4 red blood cell casts, while the erythrocyte sedimentation rate and C-reactive protein level were within normal limits. Anti-Saccharomyces cerevisiae (ASCA) IgG antibody was 76.2 U (positive >10 U) and IgA was 13.2 U (negative). His antinuclear antibody titer was 1:80 (positive) with a speckled pattern.

Tests for double-stranded DNA antibody, Sjogren Syndrome A for extractable nuclear antigen antibodies, Sjogren Syndrome B for extractable nuclear antigen antibodies, anti-scleroderma antibody, Jo-1 antibodies, anti-ribosomal P protein antibodies, beta 2 glycoprotein (IgM and IgG), cryoglobulinemia, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, hepatitis BsAg, and hepatitis C virus antibodies were all negative. Complement components C3 and C4 were normal. A brain magnetic resonance image and magnetic resonance angiogram showed multiple bilateral white matter hyperdensities and irregularity of vessels that were most likely related to vasculitis (**Figures 1A & 1B**), with evidence of petechial hemorrhage and an old small pontine infarction. Celiac and superior mesenteric angiogram showed no significant arterial abnormality. The final diagnosis was brain vasculitis secondary to CD. The patient was started on prednisolone 60 mg (Wockhardt United Kingdom Limited, Wrexham, UK) per oral once daily for one month, then tapered to 5 mg per week to 10 mg once daily, azathioprine (75 mg [Salix Pharmaceuticals Inc., Wilmington, NC, USA) per oral once daily, mesalamine 1-g (Pentasa, Ferring, Denmark) per oral twice daily, and calcium, and vitamin D supplements. After one week on prednisolone, the melena, abdominal pain, and skin rash resolved, and paralysis improved dramatically, with power of the left side improving from 0/5 to 4/5.

This case demonstrates vasculitis of the CNS, which is a rare extraintestinal manifestation of CD. The patient had suffered an ischemic stroke 3 months prior to the concomitant diagnosis of CNS vasculitis and CD. The resultant neurologic deficits (left hemiplegia), which were persistent after the stroke, improved dramatically after steroid therapy. For this reason, we believe that CNS vasculitis was the initial presentation of CD in our patient. However, we cannot fully explain the mechanism of stroke in this patient because other conditions such as hypertension must be taken into account. We also do not exclude the possibility of a thrombotic stroke, which has been described in patients with quiescent CD.[4]

Clinically, patients with CNS vasculitis present with symptoms, such as headache, nausea, vomiting, confusion, and signs of neurological deficits.[5] Certain clinical features, such as constant fever, glomerulonephritis, palpable purpura, peripheral neuropathy, and ischemic peripheral vascular symptoms, should alert the physician to a systemic

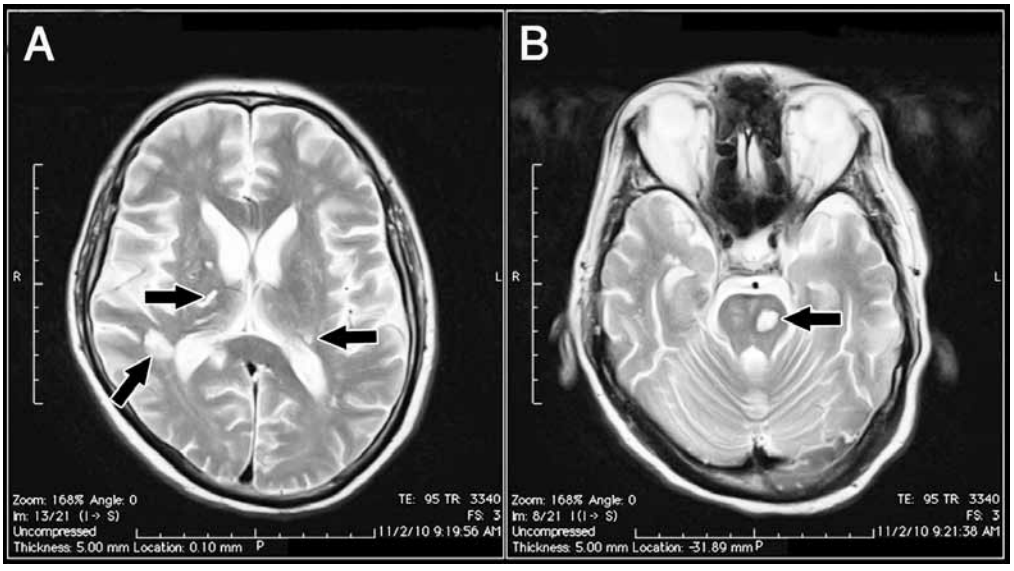

Figure 1 - Axial T2W image through the corona radiata and pons. **A**) multiple white matter hyperintensities denoting infarcts of variable ages. The lesion in the thalamus shows a dark hemosiderin rim. **B**) There is a large left para-sagittal hyperintense lesion in the pons representing a chronic infarct with a thin dark hemosederin rim. The hemosederin rim suggests previous hemorrhage.

involvement. In general, blood tests are normal and occasional findings such as anemia, leucocytosis, high erythrocyte sedimentation rate and C-reactive protein level, or a positive autoimmune screen might suggest systemic vasculitis.[5] Rheumatoid factor and vasculitis-associated antibodies are inconstantly found in patients with CD-associated vasculitis. On imaging studies of the brain, CNS vasculitis is characterized by evidence of multiple ischemic lesions of different ages, and non-specific T2-hyperintense white matter lesions. Our patient presented with symptoms of CNS vasculitis and new skin lesions that were shown to be cutaneous vasculitis. Although brain biopsy was not carried out in our case, CNS vasculitis seemed the most likely diagnosis because of the patient's presenting symptoms, signs that suggested CNS vasculitis on brain imaging, and rapid clinical improvement after administration of prednisolone.

The diagnosis of CNS vasculitis can be very challenging to physicians because the clinical presentation is usually diverse, and the condition is mimicked by many other illnesses. Imaging techniques are not reliable and are only helpful in supporting the diagnosis.[5] Cerebral angiography has proven useful in evaluating patients with CNS vasculitis, and it can support the diagnosis or suggest the need for a biopsy; however, biopsy of the brain remains the gold standard in the diagnosis of CNS vasculitis.[5]

Different treatment options have been explored in the management of CNS vasculitis. Generally, a combination of steroids and cytotoxic drugs are recommended in the treatment of CNS vasculitis. The practical approach is typically to control the disease with high-dose steroids for approximately one month, and then add cyclophosphamide only if there is a failure with steroids, or the patient starts to develop signs of adverse effects to steroid treatment. Our patient showed a good response to standard therapy with prednisolone, and there was no indication for treatment with cyclophosphamide.

In summary, vasculitis of the CNS is rarely associated with CD. Systemic vasculitis could be secondary to CD, which may appear late after stroke and cerebral vasculitis. Its diagnosis can be challenging for physicians, especially if it precedes the diagnosis of CD. Hence, to avoid overlooking associated disorders, physicians should have high clinical and diagnostic skills.

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