Stroke revealing celiac disease associated with multiple arterial thrombotic locations

Accident vasculaire cérébral révélant une maladie cœliaque associée à de multiples localisations thrombotiques artérielles

Case report
A 40-year-old woman presented with sudden-onset right hemiparesis and aphasia. She had no particular past medical history besides smoking (10 packet-years) and using progesterin-only oral contraception. On examination, she was underweight with a body mass index of 18. Neurological examination revealed mutism with Broca’s aphasia, right central facial palsy, right upper limb paresis and paresthesia, right lower limb ataxia, pyramidal tract signs with bilateral Babinski signs, and depressed but symmetrical deep tendon reflexes. Examination of other organs, including cardiovascular examination, was unremarkable, and the distal pulses were palpable with no murmur. Magnetic resonance imaging of the brain demonstrated an ischemic lesion in the superficial and deep territory of the left middle cerebral artery and hemorrhagic transformation within the infarction. The electrocardiogram, Doppler examination of the supra-aortic vessels, transthoracic Doppler echocardiography, and transesophageal echocardiography were normal. Doppler ultrasound of the lower limb arteries revealed focal thrombosis in the infrarenal aorta and a recanalized thrombus in the left popliteal artery. The ankle-brachial index was 0.66 on the left side. Computed tomography angiography of the aorta confirmed a mural thrombus extending over a height of 3.4 cm from 3.5 cm below the left renal artery (figure 1). The complete blood count revealed non-regenerative microcytic hypochromic anemia (hemoglobin: 104 g/L). Other abnormal laboratory findings were low serum albumin (23 g/L) without proteinuria, profoundly depleted serum ferritin (4 mg/L), and low vitamin B9 (2.6 μg/L). Glycated hemoglobin, serum electrolytes, CRP, and the coagulation, thyroid, liver, and lipid panels were normal. Thrombophilia screening was negative (no activated protein C resistance, absence of mutation of factor II or V, absence of circulating lupus anticoagulant, absence of anti-B2GP1 or anticardiolipin antibodies, no antinuclear, anti-native DNA antibodies, and normal levels of antithrombin III, homocysteine, and proteins C and S). Given this malabsorption syndrome despite sufficient nutritional intake, celiac disease was suspected. This diagnosis was confirmed by the presence of both high levels of anti-transglutaminase IgA antibodies (> 100 μg/L) and total villous atrophy on fundal and duodenal biopsy. A strict gluten-free diet and supplementation with iron, folic acid, and vitamin D were introduced. For the purpose of secondary cardiovascular prevention, long-term antiplatelet therapy (aspirin, 75 mg) was prescribed.

Discussion
Celiac disease (CD) is a common gastrointestinal disorder that occurs in genetically predisposed individuals [1]. The literature contains several reports of thrombotic disorders in patients with CD. These patients appear to have an increased risk of venous thromboembolism, i.e., deep vein thrombosis and its complication, pulmonary embolism [2]. Rare cases of portal vein or hepatic vein thrombosis (Budd-Chiari syndrome) have been also described [3]. There have been reports of arterial thrombosis, such as myocardial infarction [4], mesenteric infarction [5], and ischemic stroke [6–8]. Thus, the risk of stroke is moderately increased in the year after diagnosis and then decreases (HR 1.45, 95%CI [1.12–1.86]; P = 0.004) [6]. To our knowledge, this is the first report of a multiple arterial thrombotic case associated with a CD. The cause of the vascular disorders seen in patients with CD remains controversial [9]. The presence of thrombophilic risk factors for thrombosis, such as protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies, was reported depending on the case, although, our patient had none of these thrombophilic factors. One theory is that the strokes observed in CD may be a consequence of autoimmune vasculitis in the vessels supplying the central nervous system [8,10,11]. When gliadin (a gluten protein fraction) penetrates the intestinal mucosa, it is believed to bind to the enzyme tissue transglutaminase (tTG). In genetically predisposed individuals (HLA DQ2-DQ8), the gliadin-tTG complex appears to trigger a humoral autoimmune reaction, involving the production of anti-gliadin and anti-tTG antibodies and lymphocyte proliferation. The tTG present in brain tissue plays an important role in maintaining endothelial integrity and in neuron metabolism. Anti-tTG antibodies may bind to TG in the endothelium of the cerebral vasculature, causing autoimmune angiopathy, leading to cerebral ischemia. Other mechanisms have been postulated, such as malabsorption-induced vitamin deficiencies (homocysteine and related B-vitamin deficiencies). Thus, Gluten exclusion in
CD improves folate status and normalizes homocysteine concentrations [12]. The fact that our patient was young and no cardioembolic causes could be identified, and that all of the laboratory assessments for inflammation, thrombophilia, and immunological causes were negative, points to a probable causal relationship between celiac disease and arterial thrombotic events. However, the peculiarity of this case was the nature of the macrovascular disease, combining an aortic mural thrombus, popliteal artery thrombosis and cerebral thrombosis, which were clearly identified by computed tomography angiography. The role of the patient’s CD in these disorders is highly probable, given that she was a very moderate smoker and that, in principle, progestin-only oral contraception does not increase the risk of thrombosis.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References