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Title: A rare cause of neurologic complains

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We present a case of a 66 year old man with complains of bilateral hearing loss, dizziness, postural imbalance, headache, dysphagia, slight decrease of strength on the right superior limb, limitation of neck mobility, non-quantified weight loss and reduced visual acuity, with four months evolution.

He had a previous history of a lumbar hernia 29 years ago, and an infectious disease that he could not specify, 25 years ago. Because of that infection he was medicated with antibiotics (Bacitracin) for 3 years. At presentation he had no history of recent infectious diseases and denied fever, diarrhoea, arthralgia or myalgia. He denied alcohol intake or smoking and didn't have a significant personal or familial medical history.

Clinical examination showed posterior cervical contracture without meningeal signs, gait imbalance, right brachial hyperreflexia. Ocular examination revealed bilateral papilla oedema with vitritis, floaters, retinal haemorrhages and reduced visual acuity.

Peripherical blood was collected and laboratory test revealed a mild anaemia (haemoglobin 10.8 g/dL), and an inflammatory syndrome [(C-reactive protein (CRP) 91.3 mg/L] with no other alterations. Lumbar puncture was normal.

Image exams revealed a leukoaraiosis (chronic vascular disease) on cranial MRI. CT Scan showed no abnormalities.

Patient was admitted for further investigation.

Tumour markers, auto-immune antibodies, infectious serology, and Mantoux test were all negative.

Six days after admission a new brain and cervical MRI was performed and a recent small right ischemic cerebellar stroke was found; ocular globes had no alterations and the spinal cord showed alterations consistent with cervical myelomalacia (degenerative signs).

Renal ultrasonography, protein electrophoresis, 24h urine protein, urine Bence Jones protein test and aquaporin antibody were all normal.

Thorax CT Scan revealed bilateral axillary, retrocrural, celiac artery chain and small gastric curvature adenopathies and on physical examination, left supraclavicular and right inguinal adenopathies were palpable.

Excisional biopsy was performed for one of the slightly enlarged inguinal lymph nodes.

MICROSCOPIC FINDINGS

Lymph nodes showed marked distension of sinuses with a diffuse histiocytic infiltrate. The paracortex and medullary areas were largely replaced by histiocytes, with a few small residual germinal centres present within the cortex and variably sized lipid vacuoles within the sinuses. There was no evidence of well-defined granuloma formation or necrosis. The periodic acid-Schiff stain with diastase (PAS-D) showed strong positivity due to sickle-shaped particles filling the cytoplasm of the histiocytes, while Ziehl-Neelsen stain for mycobacteria was negative.

PROPOSED DIAGNOSIS

WHIPPLE'S DISEASE

DISCUSSION

We present a case of a 66 year old man with neurologic complains. Different hypothesis of diagnosis were made, namely space occupying lesion of the brain, CNS infection, malignant tumors, auto-immune diseases and neuromyelitis optica (Devic disease). All these hypotheses were ruled out with laboratory and image exams and the diagnosis of Whipple Disease was made on histologic examination of peripheral lymph nodes on a patient with chronic vascular cerebral alterations and degenerative spinal signs.

Whipple's disease (WD) was first reported in 1907 and is named after George H. Whipple who first described an intestinal "lipodystrophy" [1]. It's a rare disease, with an estimated annual prevalence of 1:1,000,000, mostly affecting middle-aged Caucasian men [3]. This is a chronic multiorganic bacterial infection caused by *Tropheryma whipplei* - a gram-positive bacterium that usually involves the gastrointestinal tract but may also affect the mesenteric, abdominal, peripheral lymph nodes, CNS as well as other
tissues [2].

WD has a highly variable systemic presentation and the patient didn't present with the most common features that include weight loss, diarrhea, and arthralgia/arthritis[4].

Patient showed neurologic involvement of WD with Neuro-ophthalmic findings (bilateral papilla oedema with vitritis, floaters, retinal haemorrhages and reduced visual acuity) with no neurological deterioration (cognitive changes, dementia, depression, and personality changes) the most frequent neurologic signs [4]. CNS involvement occurs in about a third of patients, and portends a worse prognosis, as more than 25% die within four years [4].

Although Whipple's disease confined to the CNS is rare, the CNS is the most common site of disease relapse and because of that, long-term treatment with antibiotics that are able to cross the blood-brain barrier should be started, after the first onset of the disease. In these cases, CT scans and MRI of the brain are often normal, as in the case that we present.

The patient reported 29 years ago an infectious disease that he could not precise, after a proximal GI tract biopsy, having to take antibiotics for 3 years. Most likely the diagnosis at that time was WD that relapsed at the present with CNS symptoms.

The patient had mesenteric lymph nodes, which occurs in 52% of patients and peripheral lymphadenopathy witch is a rare finding [6]. Peripheral biopsy of lymph nodes was performed, were the diagnosis of WD was possible.

The diagnosis of WD is established most frequently by a biopsy of the small intestine, which commonly shows a marked histiocytic infiltration of the lamina propria. However, lymph nodes may be the initial and/or the only material available for microscopic examination. Involved lymph nodes generally show numerous lipid vacuoles, an increased number of foamy macrophages with finely granular appearance, and granulomatous inflammation with or without foreign body–type giant cell formation.

Histologic differential diagnosis should include MAI infection or other histiocytic infiltrates, including silicone lymphadenopathy, lipogranulomatosis, lymphangiogram effect, and storage disorders that can morphologically mimic Whipple disease. The mycobacteria in MAI infection are acid-fast and PAS positive, while *Tropheryma whipplei* is acid-fast negative. Rarely, histologic features of Whipple disease may mask features of sarcoidosis including lymph nodes in that well-formed nonnecrotizing granulomas are noted [7].

Historically, the diagnosis of Whipple disease was based on the histologic findings and electron microscopic demonstration of the bacterium. In the present times, an increasing number of molecular assays have been developed. Although other ancillary tests have been used to detect the causative organism in Whipple disease, PCR seems to be becoming the test of choice for confirmation. PCR gives a determination of the nucleotide sequence 16S rRNA gene of *Tropheryma whipplei*. Results have to be correlated with clinical setting as well as with conventional histology and special stains, as PCR has a high sensitivity but low specificity [8, 9, 10].

The natural course of Whipple's disease is fatal, without prolonged antibiotic therapy. Nowadays, the prognosis is good, although the ideal antimicrobial regimen is not yet found. After diagnosis of WD, patient started antibiotherapy and corticotherapy with remission of symptoms.

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