

Giant intracranial xanthoma with blurred vision as the first symptom: a case report and literature review

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A 31-year-old male noticed the blurred vision in his right eye for five days with no obvious predisposing causes, accompanied by mild dizziness; no headache, nausea or vomiting was reported. The patient was admitted to the Department of Ophthalmology. No obvious nodular lesions were found in the body. The patient's binocular visual acuity was 20/20. There were no obvious abnormalities in the eyelid, conjunctiva, cornea, anterior chamber, iris, or lens of either eye. The pupils of both eyes were 2.5-mm in diameter, and both reacted directly and indirectly to light stimulation. Fundus photography showed the optic nerve swelling and radial superficial retinal hemorrhage of the both eyes (Fig. 1a-1b). Blood panel, urine routine, liver and kidney function were all normal. Total cholesterol (4.03 mmol/L), triglycerides (1.31 mmol/L), high density lipoprotein (1.19 mmol/L) and low-density lipoprotein (2.03 mmol/L) were all in the normal limits.

Head MRI was performed, showing a mass in the right temporal lobe, clear boundary, and multiple separations, which thinned and disappeared closer to the skull. The lesion was slightly dilated, and the size of the lesion was presumably be measured as 5.1 cm × 5.9 cm × 8.4 cm. The right temporal lobe and lateral ventricle were all compressed, with the midline structure shifted to the left (Fig. 2a-2b). The patient was then transferred to Neurosurgery. During the operation, we observed that: the skull around the tumor area was partially protruding; the tumor had invaded the skull; the adhesion of tumor and skull was tight. The actual size of the tumor was 5.6 cm × 7.5 cm × 10.1 cm, and the texture was soft and gelatinous (Fig. 3). Histological analysis revealed foam cell accumulation in the mucous connective tissue of the right temporal lobe (Fig. 4). The immunohistochemistry results were as follows: CD34 (+), CD99 (+), EMA (-), GFAP (-), IDH-1 (-), Ki-67 (+) index about 10%, Oligo-2 (-), PR (-), S-100 (-), Vim (+), β-Catenin (+), CD1a (-),

CD68 (+).

Three months after surgery, the visual acuity of both eyes was 20/20; The visual fields were normal, the optic disc edema and retinal hemorrhages had disappeared (Fig. 1c-1d). MRI indicated the midline structure was back to normal (Fig. 2c-2d). Informed consent from the patient was obtained to report this case.

Discussion

Xanthomas are produced by the accumulation of foam cells, in skin, fascia and connective tissues, which originate from the oxidation of macrophages overloaded with low-density lipoprotein particles. Xanthomas can be divided into hyperlipidemia xanthoma, non-hyperlipidemia xanthoma and necrobiotic xanthogranuloma (NXG) [1]. Xanthomas have a variety of clinical manifestations, which can be soft to semisolid skin spots or papules, the most common of which are giant yellow nodules. Both hyperlipidemia xanthoma and non-hyperlipidemia xanthomas contain lipids (unesterified cholesterol, cholesterol ester and phospholipid) and collagen, and a large number of foam cells can be observed by histological examination, whereas progressive collagen necrosis, cholesterol crystal fissures and lipid vacuoles can be seen in the tissue examination of NXGs. Lipids spread through the vascular wall into the surrounding connective tissues, and macrophages devour low-density lipoprotein particles and lipid complexes with liposomes. Since cholesterol cannot be degraded, it accumulates in these cells, to generate foam cells. The different proposed mechanisms include: 1) high local lipid concentration, 2) different types of lipoprotein at normal blood lipid concentration, 3) lipid exosmosis increases (vascular permeability increases, local circulation increases, or chronic inflammation), 4) lipid *in situ* synthesis and deposition in tissue cells, and 5) reverse cholesterol transport dysfunction [2–4].

Xanthomas mainly occur in subcutaneous tissue and are related to local injury, thus they often occur in the buttocks, elbows, eyelids and hand creases, as well as in the Achilles tendon and extensor tendon of the hands [5]. Xanthoma of the eyelid is the most common type of xanthoma [6]. Intracranial xanthomas are extremely rare; although they are benign tumors, intracranial xanthomas can develop continuously and may lead to intracranial nerve injury. Intracranial xanthomas have been reported to occur mostly in the temporal bone and skull base, and mostly in middle-aged and elderly patients, with few in young patients. The location and scale of the lesion determines the clinical manifestations, and the reported symptoms include severe headache, ear discharge, cranial nerve palsy, tinnitus, and otitis media [5]. Imaging features can help in the diagnosis of intracranial xanthomas: computed tomography findings are low-density masses outside the dura mater, scattered calcification, skull bone destruction and bone sclerosis at the edge of the lesion. MRI is characterized by adipose tissue signal-based lesions, and uneven signal intensity, with a strip of arc-like low-signal separation and enhancement. The periventricular masses showed equal- or high-

intensity signal on MRI, resulting from the high lipid content [5]. Although imaging can effectively help with the identification of lesions, intracranial xanthoma is not always considered firstly because of its rare occurrence. Misdiagnoses happen frequently and the final diagnosis often depends on the pathological examination after resection.

Xanthomas are associated with a variety of diseases, especially lipid-storage and -metabolism disorders, which often occur in patients with type II hyperlipidemia. Since its mechanism is similar to that of early atherosclerosis, xanthoma has received more attention in recent years. A prospective study, which followed nearly 13000 subjects for more than 20 years, found that, even after adjusting for covariables such as age, gender, diabetes, smoking, hypolipidemic therapy and postmenopausal status, the occurrence of xanthoma was associated with: a significant increase in the risk of myocardial infarction (48% increase); ischemic heart disease (38% increase); and lower-extremity ischemic disease (70% increase) [6]. To-date, most of the reported intracranial xanthomas have been characterized by hyperlipidemia, especially type II hyperlipidemia. There was also a report of a young patient with bilateral disc swelling caused by intracranial xanthoma. But, the patient had severe hyperlipidemia, and the patient's mother and two sons had elevated blood lipids [7]. However, the blood lipids of the patient in this case were normal.

Based on a case of NXG with severe hypocholesterolemia, Matsuura *et al.* suggested that NXG may start when activated monocytes degrade modified low-density lipoprotein through pathways other than CD36 or the type A scavenger receptor, and accumulate a large amount of lipid *in vivo*. The activation of monocytes may lead to the accumulation of lipids derived from intracellular lipoprotein, leading to non-hereditary xanthoma and obvious hypocholesterolemia [8]. In a case of skin xanthoma with no hyperlipidemia, reported by Feingold *et al.*, it was suggested that the monoclonal antibody immunoglobulin G (IgG) of the patient interacted with apolipoprotein B-100, but did not alter the metabolism of the lipoprotein through the LDL receptor pathway [9]. In addition, mixing the monoclonal antibody IgG of the patient with normal LDL led to normal LDL increasing the lipid effect of macrophages on cholesterol. Therefore, they suggested that the monoclonal antibody IgG-LDL complex interacted with macrophage scavenger receptors, resulting in xanthoma in the context of normal blood lipids [9]. In addition, a case reported by Abrams *et al.* showed that cholesterol accumulation in tissues is caused by abnormal lipoproteins, rather than by excessive plasma cholesterol [10]. However, intracranial xanthoma was not found in those cases, so the pathogenesis of the present case cannot be fully explained.

Most patients with xanthoma need surgical treatment, to relieve the space-occupying effect. For patients with dyslipidemia, systemic hyperlipidemic agents should also be used. However, the patient in this case showed a non-hyperlipidemia xanthoma, so only conservative resection of the mass and implementation of a low-fat diet were necessary; no systemic lipid metabolism interventions were required. The improvement of the eye condition in this patient was closely related to the removal of space-occupying effect in brain. The pathogenesis of non-hyperlipidemia

intracranial xanthoma has not been fully determined, which highlights the need for long-term study and further discussion. Meanwhile, huge intracranial xanthoma presenting with blurred vision as the first symptom is rare. In this case, the right temporal lobe was substantially occupied, as the maximum transverse diameter of the tumor was about 10.1 cm; the patient had no systemic symptoms, and only had mild head discomfort. No characteristic imaging findings were identified, and the final diagnosis relied on pathological examinations.

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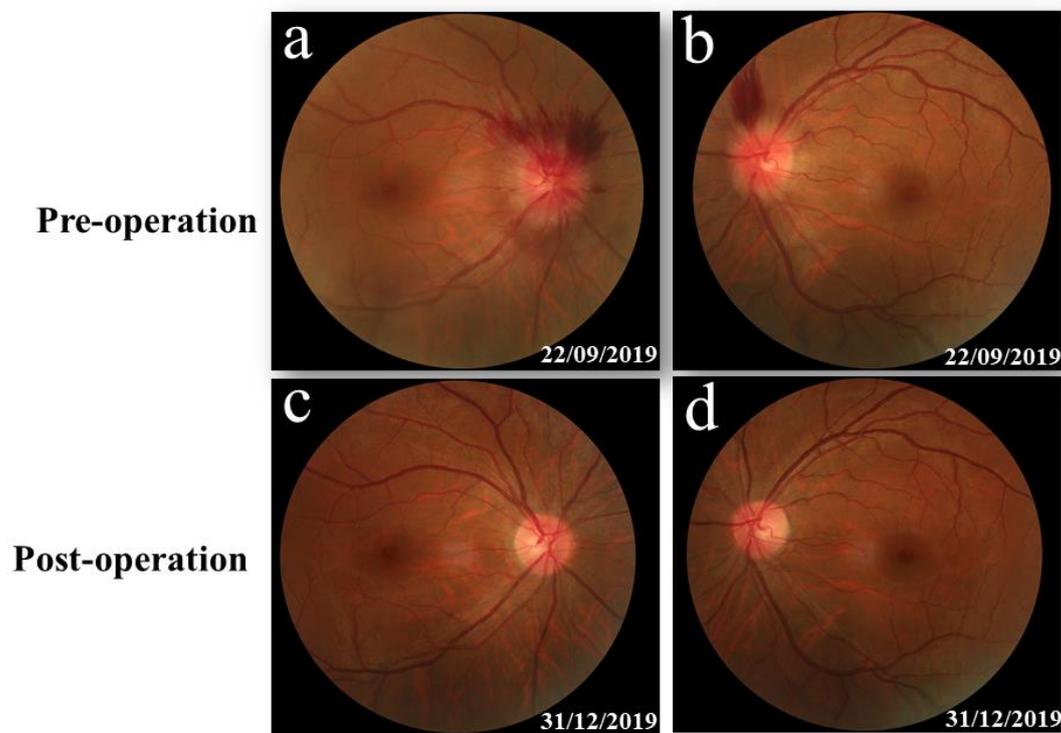
Figures:

Figure 1. Fundus photography. The swelling and blurry boundaries of both optic nerves were present (a-b). There was a splinter radial superficial retinal hemorrhage above the optic disc; no other obvious abnormality was observed (a-b). Three months after surgery, all these symptoms, including optic nerve swelling and retinal hemorrhage disappeared (c-d).

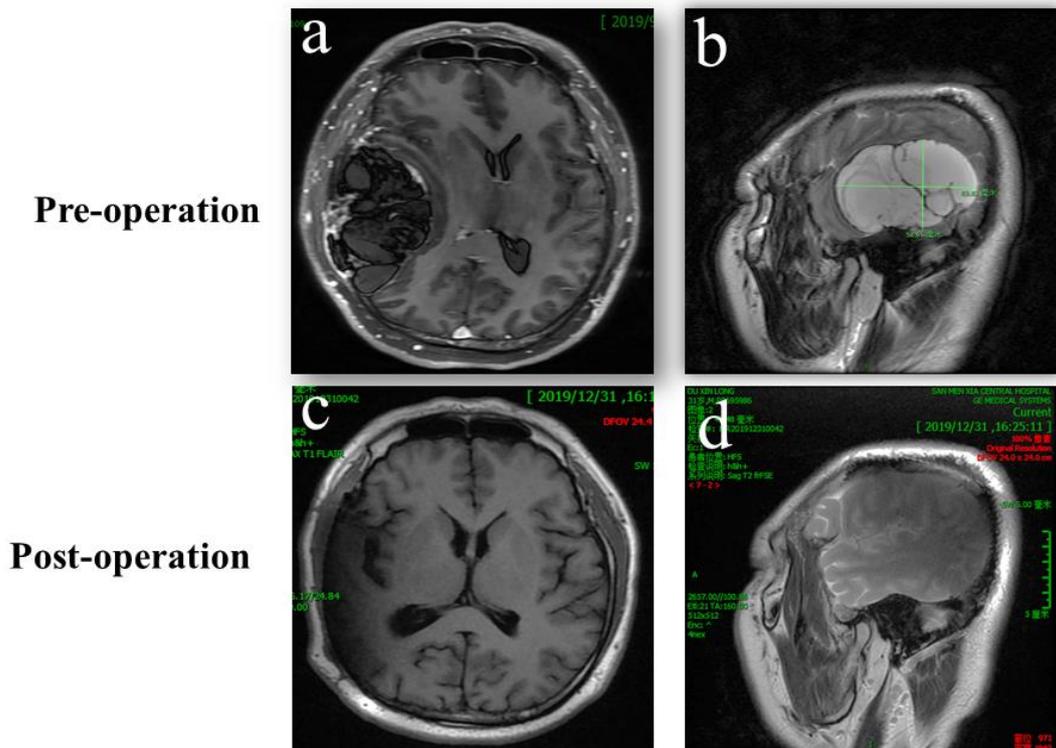


Figure 2. Head MRI. A mass in the right temporal lobe, a clear boundary, and multiple separations, which progressively thinned when near the skull. The right temporal lobe and lateral ventricle were suppressed, with the midline structure shifting to the left (a-b). Three months after surgery, MRI indicated the midline structure was back to normal (Fig. 2c-2d).



Figure 3. Surgical observations. The skull in the tumor area was partially protruding, the tumor invaded the skull, the adhesion of tumor tissue and skull was tight and the brain tissue of the right temporal lobe was compressed (a). The actual size of the tumor was $5.6 \times 7.5 \times 10.1$ cm, and the texture was soft and gelatinous (b, c).

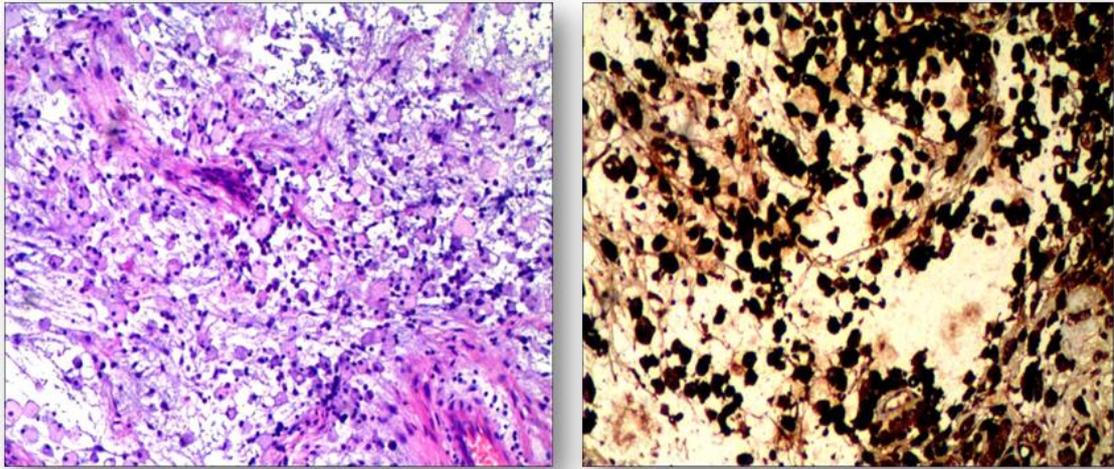


Figure 4. Hematoxylin and eosin staining. Foam cell accumulation in the mucous connective tissue of the right temporal lobe.