Bilateral frontal intracranial xanthoma associated with type II hyperlipidemia in a 42-year-old woman: illustrative case

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BACKGROUND Xanthoma is a granulomatous lesion that develops as a result of leakage and accumulation of serum lipoprotein from the circulatory system into the surrounding tissue. Although it is commonly manifested superficially in the exposed surface as a subcutaneous xanthoma, xanthelasma, or arcus cornea, an isolated intracranial xanthoma is an unusual finding and is usually misdiagnosed. Because of its rarity, there is no exact prevalence of this lesion, which is only reported in some cases. Intracranial xanthoma is also rarely found in patients with hyperlipidemia, although the most common occurrence is in patients with type II. To the best of the authors’ knowledge, no previous studies or literature has reported bilateral involvement of intracranial xanthoma in the frontal lobe.

OBSERVATIONS The authors reported an unusual case of bilateral involvement of intracranial xanthoma in the frontal lobe with associated type II hyperlipidemia in a 42-year-old woman. Macroscopically, the tumor had an appearance of greyish-yellow color with a brittle, solid consistency. Histopathological examination revealed numerous lipid-laden macrophages surrounded by a cystic, necrotic, partially hemorrhagic area, with some parts consisting of hemosiderophages and proliferative capillary blood vessels. The histopathological findings indicated the characteristics of xanthoma.

LESSONS Bilateral frontal intracranial xanthoma with associated type II hyperlipidemia is an unusual finding. Despite its rarity and wide variety of radiological presentations, it should be considered one of the differential diagnoses of lesions that develop intracranially and intraxially. Confirmation with histopathological examination is needed to exclude from other differential diagnoses.

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KEYWORDS intracranial tumor; intracranial xanthoma; neurosurgery; oncology

Xanthoma is a granulomatous lesion that develops as a result of leakage and accumulation of serum lipoprotein from the circulatory system into the surrounding tissue.1,2 Although it is commonly manifested superficially in the exposed surface as a subcutaneous xanthoma, xanthelasma, or arcus cornea, an isolated intracranial xanthoma is an unusual finding and is usually misdiagnosed.2–4 Because of its rarity, there is no exact prevalence of this lesion, which is only reported in some cases. Intracranial xanthoma is also rarely found in patients with hyperlipidemia, although the most common occurrence is in patients with type II.3,4 To the best of the authors’ knowledge, no previous studies or literature has reported bilateral involvement of intracranial xanthoma in the frontal lobe.

We present a case report of bilateral frontal intracranial xanthoma that developed in a 42-year-old woman with associated type II hyperlipidemia. We provide a detailed description of the clinical course, physical and supportive examinations, histopathological findings, and management strategies as well as a review of this case based on previously reported studies and literature.

Illustrative Case

History

A 42-year-old woman presented to the neurosurgery clinic with a 2-year history of recurrent seizures. Her seizures are characterized by shaking all the extremities and being unconscious during each attack. They develop at least two to three times a week and last approximately 5 to 10 minutes. The patient also reports severe chronic headaches since 4 years ago, which feel like pressure of a heavy load in her head, especially over the forehead region. There are no symptoms such as nausea or vomiting, behavioral disturbance, weakness, sensory complaints, or

ABBREVIATIONS CT = computed tomography; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging.

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The presence of bumps in any parts of the body. The patient has a history of uncontrolled hyperlipidemia. No history of xanthoma was found in any of the patient's relatives.

**Examination**

The visual analog scale and Karnofsky performance scale ratings were 6 and 80, respectively. No abnormalities were found on general and neurological examinations. No manifestations of xanthoma were found, such as subcutaneous and tendon xanthoma, arcus cornea, or xanthelasma of the eyelid. The lipid profile shows a significant levels of serum low-density lipoprotein (183 mg/dL) and serum cholesterol (265 mg/dL), with a normal serum triglyceride level (194 mg/dL).

Based on the patient's history, we suspected an underlying intracranial space-occupying mass lesion, so we referred the patient to another province with magnetic resonance imaging (MRI) because there are no such facilities in East Nusa Tenggara.

MRI was performed, wherein the contrast-enhanced T1-weighted, unenhanced T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences showed a focal mass with heterogeneous signal intensity in the frontal lobe of both hemispheres, especially on the right side (Fig. 1A–D). The mass consisted primarily of a cystic component with some vascularized and necrotic area, surrounded by edema. There was no significant enhancement with intravenous contrast administration. Multiple small cystic components extended between the fornix and corpus callosum (Fig. 1C and D). Based on characteristics of MRI, we suspected a malignant glioma, oligodendroglioma, lymphoma, or other intraxial lesion as the primary differential diagnoses. We performed a surgical procedure to help relieve the symptoms and obtain a histopathological analysis of the underlying mass.

**Operative Procedure**

We performed a horseshoe-shaped incision around the midline structures to expose both hemispheres. The lesions were approached interhemispherically, with high preservations of the superior sagittal sinus and draining cortical veins. We performed a subtotal resection of the mass in both frontal lobes, leaving unresectable structures between the fornix and corpus callosum. The mass was examined further at the pathology anatomy laboratory. The dura was then closed with a watertight closure technique and fibrin glue. The bone flap and skin were closed with sequential technique. The procedure lasted approximately 4 hours.

**Histopathologic Features**

We obtained two specimens, 1 × 0.5 × 0.3 cm and 5 × 2 × 2 cm. Both specimens had a macroscopic greyish-yellow color with a brittle, solid consistency (Fig. 2). The microscopic appearance showed plenty of xanthoma cells characterized by numerous lipid-laden macrophages, surrounded by a cystic, necrotic, and hemorrhagic area (Fig. 2). Some parts consisted of hemosiderophages and proliferative capillary blood vessels. No evidence of malignancy was found in either specimen. Based on the histopathological findings, both specimens showed characteristics of intracranial xanthoma. The specimen was examined with hematoxylin and eosin stain (original magnification ×100).

**Postoperative Management**

We obtained a postoperative contrast computed tomography (CT) scan, and the lesions in both frontal lobes were completely resected with some residual masses around the fornix and corpus callosum. The patient was given a statin class drug (atorvastatin 20 mg) and recommended lifestyle modifications to help control hyperlipidemia. She was discharged on postoperative day 6; during the days of observation, there were no associated symptoms such as seizure, headache, or new neurological deficit. She lives on a remote island in East Nusa Tenggara, so we can only follow up with her by phone. We have followed the patient for at least 5 years, during which period there have been no reports of new or recurrent symptoms, and she can perform daily activities without any limitations. There are no facilities to provide imaging modalities such as CT or MRI in nearby health care facilities, so any change of the residual mass cannot be ascertained.
Discussion

Observations

Xanthoma is mainly associated with abnormal lipid storage or metabolism, which causes increased serum lipid level or hyperlipidemia. There are five types of hyperlipidemia; types II and III are caused by biochemical abnormalities that cause an increase in circulating lipoprotein with associated high serum cholesterol levels. In contrast, types I, IV, and V are caused by lipoprotein lipase deficiency and other glycoprotein abnormalities with associated high serum cholesterol and triglyceride levels. Intracranial xanthoma is rarely found in patients with hyperlipidemia, although the most common occurrence is in patients with type II. Development of intracranial xanthoma in the absence of hyperlipidemia can occur in histiocytic disorders such as xanthoma disseminatum.

The development of xanthoma begins with leakage of serum lipoprotein and cholesterol from the circulatory system into the surrounding tissue, which activates the macrophages to phagocytize it. However, lipoprotein and cholesterol content cannot be degraded, thus forming a lipid-laden macrophage containing high lipid levels within the cytoplasm. The extracellular cholesterol levels that are not phagocytized by macrophages will crystalize and induce an inflammatory process that causes fibrosis. Xanthoma is frequently found in areas around the Achilles tendon, patella, hand extensor, and other exposed areas such as the cornea, eyelid, hand crease, elbow, and buttocks. The most common manifestations are subcutaneous and tendon xanthoma, arcus cornea, and xanthelasmas of the eyelid. There is no known direct involvement of genetic or familial factors in developing intracranial xanthoma, but they increase the chance of hyperlipidemia as one of the risk factors for xanthoma formation.

Isolated intracranial xanthoma has rarely been reported and usually presents extraaxially in the calvaria or skull base or around the convexity. Intraxially, some cases have involved xanthoma development in either the supra- or infratentorial compartment. Intracranial xanthoma rarely develops bilaterally. Based on reported studies and literature, there have been no cases of bilateral involvement of intracranial xanthoma in the frontal lobe. Signs and symptoms varied based on where the lesions grew, beginning with headache, seizures, behavioral changes, otorrhea, tinnitus, otalgia, or cranial nerve deficit. In our case, we reported an intracranial intraaxial xanthoma that developed bilaterally in the frontal lobe, and to the best of the authors' knowledge, this is the first reported case.

In general, the MRI characteristics of intracranial xanthoma resemble a high lipid content of the lesions. On unenhanced T1-weighted images, most lesions show high signal intensity, followed by low signal intensity on T2-weighted images. There is a variable enhancement with intravenous contrast administration. In our case, contrast T1-weighted images show no significant enhancement, followed by heterogeneous signal intensity on T2-weighted and FLAIR images in both frontal lobes, with some extension to the area between the fornix and corpus callosum. These findings do not show characteristics of xanthoma but rather show similar imaging features of other lesions around the frontal lobe, such as malignant glioma, oligodendroglioma, other primary brain tumors, or metastatic processes.

Histopathological examination is the main modality for diagnosing intracranial xanthoma, mainly because of its various imaging features and unpredictability due to the rarity of this lesion. In our reported case, we found a greyish-yellow mass with a brittle, solid consistency, which showed microscopic features of numerous lipid-laden macrophages surrounded by a cystic, necrotic, partially hemorrhagic area and some parts that consisted of hemosiderophages and proliferative capillary blood vessels. Based on the literature and reported studies, these histopathological findings show characteristics of xanthoma.

Intracranial xanthoma should be considered one of the differential diagnoses of lesions that developed intracranially and intraaxially. Histopathological examination is the main modality for confirming diagnosis of intracranial xanthoma. Control of underlying hyperlipidemia and early recognition of this lesion are needed, especially to avoid extensive lesion growth to prevent gross total resection. We have some limitations, such as no immunohistochemistry examination and limited follow-up imaging data. Our patient lives on a remote island in East Nusa Tenggara with no such facilities to provide imaging, so any change of the residual mass cannot be ascertained.

Lessons

Bilateral frontal intracranial xanthoma with associated type II hyperlipidemia is an unusual finding. Despite its rarity and wide variety of radiological presentations, it should be considered one of the differential diagnoses of lesions that developed intracranially and intraaxially. Histopathological examination is the main modality for confirming diagnosis of intracranial xanthoma. Control of underlying hyperlipidemia and early recognition of this lesion are needed, especially to avoid extensive lesion growth to prevent gross total resection. We have some limitations, such as no immunohistochemistry examination and limited follow-up imaging data. Our patient lives on a remote island in East Nusa Tenggara with no such facilities to provide imaging, so any change of the residual mass cannot be ascertained.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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