sciendo Acta Medica Marisiensis 2018;64(4):173-176 DOI: 10.2478/amma-2018-0027

CASE REPORT

Case Presentation: Unusual Association Between Possible Bilateral Intraventricular Xanthogranulomas, Postero-inferior Cerebellar Artery Aneurysm and Thrombophilia

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Introduction: Xanthogranulomas are rare, benign, usually asymptomatic, cutaneous tumors most frequently seen in children (juvenile xanthogranulomas). Some lesions can be found accidentally at randomly performed cerebral computer tomography (CT) or magnetic resonance imaging (MRI) or even on autopsy. **Case report**: We present the case of a 44 year-old woman, known with a thrombophilic disorder (PAI-1 gene mutation, MTHFR C677T and A1298C) on chronic anticoagulant treatment. The onset of symptoms was in 2010, when she presented paresthesia and lower limbs weakness. Two years later the patient presents with severe intermittent headache and left hemicrania and a cerebral angio-MRI is performed showing a left postero-inferior cerebellar artery aneurysm and two choroid plexus intraventricular masses in the lateral ventricles. The patient developed a new symptom, dysarthria in 2014 and in 2015 has multiple episodes of loss of consciousness, interpreted as epileptic seizures. Routine blood tests were within normal range, except for a high cholesterol level. The patient was tested for autoimmune, infectious, endocrine and metabolic diseases that were negative. Surgical treatment and biopsy from the lesion was proposed, however the patient refused both procedures. **Conclusions**: There is an association between xanthogranulomas localization and the choroid plexus, the most frequent CNS origin being in the trigon of the lateral ventricle. Our case does not resemble with any other case published, mostly because the unusual presentation, symptomatology and the association between xanthogranulomas, thrombophilia and postero-inferior cerebellar artery aneurysm which were never reported before in other cases of xanthogranulomas from the literature.

Keywords: xanthogranuloma, thrombophilia, cerebral aneurysm, choroid plexus

Received 5 June 2018 / Accepted 30 October 2018

Introduction

Xanthogranulomas (XG) are rare, benign tumors, being a common form of non-Langerhans cell histiocytosis, most frequently seen in children (juvenile XG) and in the majority of cases are asymptomatic. The most usual localization of XG is the skin, with a predilection for the neck and head region, but it can affect any organ, including the central nervous system (CNS). Some lesions can be found accidentally at randomly performed cerebral computer tomography (CT) or magnetic resonance imaging (MRI) or even on autopsy.

The most frequent cerebral localization for XG is the third ventricle, followed by the lateral ventricle and exceptionally the fourth ventricle.

The real incidence of this pathology is unknown, mostly because it is frequently asymptomatic or misdiagnosed as cystic degenerations of the choroid plexus, however according to some literature data, it was estimated at 1.6-7.0% of autopsies [1-3]

Case report

We present the case of a 44 year-old woman, known with a thrombophilic disorder (PAI-1 gene mutation, MTHFR C677T and A1298C) on chronic anticoagulant treatment The onset of the current symptomatology was in 2010, when she presented paresthesia and lower limbs weakness. A spine MRI was performed showing a dorsal arachnoid cyst for which she underwent surgery, the cyst being removed, however there was no significant improvement in her symptomatology. A year later, she also presented upper limbs weakness and a second spine MRI was performed, describing a posterior spinal cord atrophy without any signs of compression (Figure 1).

In 2012, the patient presents with severe intermittent headache and left hemicrania that responded partially positive to antalgics. Cerebral angio-MRI showed a left postero-inferior cerebellar artery aneurysm and two choroid plexus intraventricular masses in the lateral ventricles. The bilateral tumors were hypointense in T1 and hyperintense in T2 and FLAIR, and without gadolinium enhancement (Figure 2). Surgical clipping for the aneurysm was performed, with the alleviation of the algic symptoms, but without improvement of the motor deficit.

The patient developed a new symptom, dysarthria in 2014 and in 2015 has multiple episodes of loss of consciousness, preceded by intense generalized headache, with no response to antialgic treatment, hiccups and occasion-

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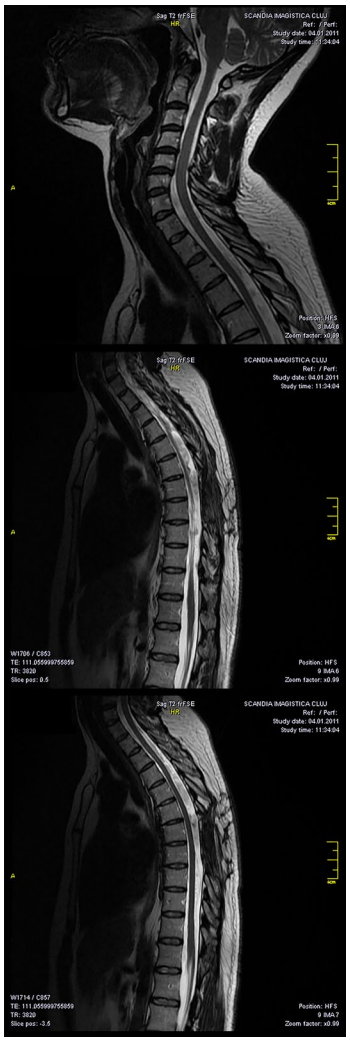

Fig. 1. Spine MRI – T2 sequence – Sagittal view

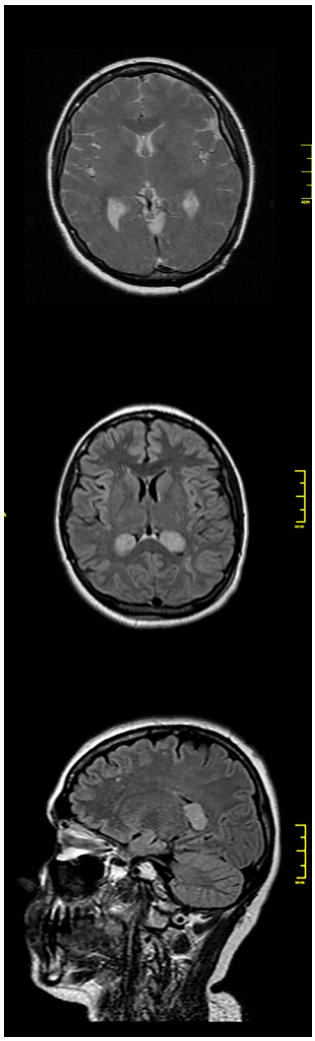

Fig. 2. Cerebral MRI – FLAIR sequence

ally vomiting with postictally aggravation of symptoms. This occurred once in two to three months with variable duration from 30 minutes up to 2-3 hours. This new symptoms were interpreted as generalized epileptic seizures. An electroencephalogram was performed, with no pathological changes.

Clinical examination revealed tetraparesis, predominantly affecting the lower limbs, ataxia, postural tremor, incoordination, brisk deep tendon reflexes, abolished abdominal reflexes, lower limbs hypoesthesia, right leg hypopalesthesia and dysarthria. No other pathological signs were found in the general examination of the patient.

In 2016 cerebral MRI was repeated showing multiple nonspecific subcortical demyelinating lesions, with no contrast enhancement.

Routine blood tests were within normal range, except for the cholesterol level which was slightly elevated. The patient was tested for autoimmune diseases (ANCA, anticardiolipin antibodies, C3, C4 complement level, ANA, Anti-dsDNA, cryoglobulins), infectious diseases (HIV, Cytomegalovirus, Toxocara canis, Ebstein Barr Virus, Lyme disease) endocrine and metabolic diseases (ceruloplasmin, plasma copper level, TSH, FT4) that were negative.

Surgical treatment and biopsy from the lesion was proposed, however the patient refused both procedures.

The patient continued anticoagulant treatment for the thrombophilic disorder and the preventive antiepileptic chronic treatment. The patient was referred to kinetotherapy and begun physical therapy.

Discussions

XG are benign tumors that occur throughout the body, however primary involvement of XG in the CNS is rare. [4,5]

Blumer described the first known case of choroid plexus XG in 1900, naming it cholestomatous endothelioma.

The prevalence of XG shows its peak between the 2nd and 4th decade of life and seems to have no sex predilection [6]. Shuangshoti et al published a small group of cases of XG (n=35) showing almost no difference between sex distribution (M:F=18:17) with more than 50% of the patients being between 20-50 years old [2]. In our case the prevalence described in the literature corresponds with the patient's profile, being a 44-year-old female.

It is not clearly understood if XG is associated with other pathologies, but in several isolated case reports there was suggested extracutaneous involvement alongside the breast [7], eye [8] and CNS [6]. In our case the patient presented an unusual association with a postero-inferior cerebellar artery aneurysm and thrombophilia, none of these pathologies being previously reported with XG. There are also no genetic mutations related with XG in the literature, even if in our case the patient had PAI-1, MTHFR, C677T and A1298C gene mutations confirmed.

The association between XG and choroid plexus has been stated in several case reports, being the most common origin point for XG masses in CNS. [9-12]

The most frequent localization of XG in CNS is in the trigon of the lateral ventricle, a less common location being the third ventricle [13,14].

XG usually remains asymptomatic, because the size of the masses is too small to obstruct the cerebrospinal fluid (CSF) flow. They become symptomatic when they have increased in size enough in order to be clinically significant by obstructing CSF flow, the most frequent symptomatic XG being located in the third ventricle where they obstruct the foramen of Monro resulting in hydrocephalus[15].

Histopatologically, XG masses consists of dense infiltrates of histiocytes with several multinucleated giant cells along with eosinophils lymphocytes and plasma cells that are often found. Cells from the altered epithelium of the choroid plexus become detached and disintegrate, releasing lipid into the choroidal matrix which will result in a xanthogranuloma. XG usually consists of cholesterol crystals, giant cells, foci of hemorrhage alongside proliferation of small blood vessels and granules of hemosiderin resulted in the process. XG pathogenesis is still debatable, several theories were issued regarding the occurrence and etiology of the disease. Some authors proposed a tissue reaction to

hemorrhage, others suggested a disturbance in lipids metabolism found in familial hypercholesterolemia and proliferation of different type of cells, while other authors like Wolf and Ayres described the "foamy cells" derived from arachnoid cells in the choroid stroma and proliferation of epithelial cells of the choroid plexus [16]. Razavi-Encha studied intraventricular lesions with electronic microscopy and noticed some leptomeningeal cells at the origin of xanthogranulomas[9].The epithelium of the choroid plexus presents cellular stratification and height reduction as they age, some of them becoming squamous. They may desquamate and increase in size becoming foamy by gathering intracytoplasmatic lipids P. Miranda et al analysed published cases until 2005 and noted fifteen cases of lateral ventricle choroid plexus xanthogranulomas and sixteen cases localized in the third ventricle, described histopathologic and radiologic findings in third ventricle masses [8]. Shuangshoti, et al resumed 35 cases of intraventricular xanthogranulomas analyzing the origin of foamy cells, symptomatology, imagery and postoperative course and stated that these intraventricular masses lead to increased intracranial pressure [2].

Chen et al performed laboratory tests and concluded a correlation between high traces of cholesterol and predisposing state in formation of xanthogranulomas of choroid plexus [17].

Regarding frequency and significance, the symptomatology encountered was: headache, nausea and vomiting, seizures, ataxia, nystagmus, double vision, hemiparesis, bladder incontinence, deterioration of consciousness, changes of personality and other symptoms secondary to intracranial hypertension [15,18]. In our case, the patient had a progressive symptomatology over the course of several years, which could not be explained by other associated pathologies, as there was no improvement after the arachnoid cyst was removed and the posterior spinal cord atrophy could explain the paresthesias, but not the limb weakness.

Deterioration of consciousness was described as a result of compression of cerebral structures and brainstem by the herniation of hippocampal gyrus or the cerebral tonsils that could lead to death [18]. In our case, the loss of consciousness was interpreted in the context of epileptic seizures, which could have been triggered by intracranial hypertension secondary to XG.

Radiologic findings showed intraventricular masses localized within the glomus of choroid plexus, in both trigones of the lateral ventricles or in the third or fourth ventricle.

In the CT scan studies, XG showed different densities in comparison to brain tissue, both hypodense and hyperdense lesions being described. When large in size, XG cannot be distinguished from other lesions such as degenerated cystic glomera by CT scan [19].

MRI performed showed in several cases hyperintense signal in T2, explained by the high solid lipidic components of XG, and also iso or hyperintense signal in T1 sequences [20].

The demyelinating lesions described in our patient's second MRI are not specific for XG and the suspicion of cerebral vasculitis was risen. In order to confirm the diagnosis, a series of tests for autoimmune, infectious and metabolic disorders were performed, which led to the exclusion of the diagnosis.

Gadolinium enhancement modifications were reported in a small number of cases, without being specific for this kind of lesion. Also, Tc^{99} scans did not show abnormal uptake [21].

Xanthogranulomas are difficult to distinguish from choroid glomerular cysts, acute infarction of the choroid plexus, papilloma, meningioma, metastatic lesions, choroid plexus carcinoma and arteriovenous malformation. Radiological differential diagnosis should be made especially with choroid cysts which have altered signal due to protein and blood products and usually follow CSF on all sequences and acute infarction of the choroid plexus, which are usually located unilateral while XG is bilateral, both having high signal on DWI [21-23]. In order to put a definitive XG diagnosis, histopathology examination is required, however in our case biopsy was proposed, but the patient refused.

The treatment is necessary only in symptomatic patients and first-line treatment is surgical intervention with mass removal. Case-reports showed that post-surgery outcome was good in unilateral XG, complications such as visual loss or death being described in patients with bilateral lateral ventricle lesions. Poor outcome was encountered in XG located in the third and forth ventricle, with a large number of postoperative complications. [24,25].

Conclusion

XG is a rare benign disease, usually found accidentally as most of the cases are asymptomatic.

There is an association between XG localization and the choroid plexus, the most frequent CNS origin being in the trigon of the lateral ventricle.

Surgery remains the standard of treatment for XG, but should only be performed in symptomatic patients, because of the associated complications that could develop after the mass removal.

Our case does not resemble with any other case published, mostly because the unusual presentation, symptomatology and the associated pathologies which were never reported before in other cases of XG from the literature.

Authors'contribution

SRA – Software, writing original draft, writing review and editing
AR – Formal analysis, validation
ZB – Formal analysis, resources, supervision, visualization
SM – Data curation, investigation
LB – Methodology, project administration, visualization
RB – Conceptualization, supervision, validation, writing review and editing

Conflict of interest

The authors have no conflict of interests.

Acknowledgement

A signed statement of informed consent to publish was signed by the patient (Nr. 18131/30.05.2016).

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