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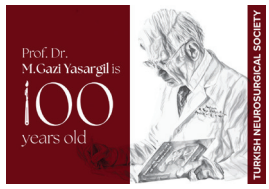

Xanthomatous Meningiomas: A Systematic Review and Case Report

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ABSTRACT

AIM: To present a systematic review and to report a case of xanthomatous meningioma, aiming to contribute valuable insights into this uncommon neoplasm.

MATERIAL and METHODS: The guiding question focused on the epidemiological characteristics of xanthomatous meningiomas. Inclusion criteria encompassed case reports or series detailing patient sex, age, and tumor location. A literature search identified 56 articles on Pubmed and Mendeley. Study selection involved independent screening by two researchers, adhering to predefined criteria. Data collection from eligible studies included patient demographics, symptoms, MRI characteristics, and immunohistochemical markers. Statistical analysis employed SPSS software for nominal qualitative and quantitative variables.

RESULTS: The case report involved a 44-year-old female presenting with disorientation and chronic headache, diagnosed with xanthomatous meningioma. The systematic review incorporated 21 studies and 27 patients, with a female predominance (55.2%) and an average age of 48.2 years. Most tumors were located in the frontal region (57.2%). Common symptoms included headache (21.4%) and seizures (14.2%). Recurrence occurred in only 7.6% of cases, emphasizing the favorable prognosis post-surgery.

CONCLUSION: Xanthomatous meningiomas, characterized by meningothelial and lipid-filled cells, remain a subject of limited research. Debates persist regarding the origin of the lipid-filled cells, whether it is from migrating macrophages or from degenerated meningothelial cells. The study highlights the epidemiology and differential diagnoses, emphasizing the importance of accurate histopathological and immunohistochemical examinations.

KEYWORDS: Xanthomatous meningioma, Systematic review, Meningioma, Skull base tumor

ABBREVIATIONS: WHO: World Health Organization, **MRI:** Magnetic resonance imaging, **CONEP:** National commission for ethics in research, **CT:** Computed tomography, **SD:** Standard deviation, **RDD:** Rosai-dorfman disease, **EMA:** Epithelial membrane antigen

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INTRODUCTION

Meningiomas are a type of primary neoplasm of the central nervous system derived from meningothelial cells located in the arachnoid, accounting for approximately 20% to 37.6% of all central nervous system tumors (25,29). They have an incidence of 1.3 to 7.8 new cases per 100,000 inhabitants per year in the USA and affect more women than men, with a ratio of 2.3:1 (19,20,21,22,34).

According to the latest 2021 classification by the World Health Organization (WHO), meningiomas can be classified into 15 variants and 3 grades of malignancy based on histopathological and immunohistochemical findings. Metaplastic meningioma is an uncommon variant, typically grade I, marked by the presence of mesenchymal tissue in the tumor—either focal or widespread—with the potential for bone, cartilage, or lipid formation (18,26,30).

Xanthomatous meningioma is a rare subtype of metaplastic meningiomas that occurs when tumor cells of meningothelial origin begin to accumulate lipids, giving the neoplasm its foamy appearance (26).

Due to the rarity of this entity, there have been few publications on this type of tumor, and there is still much discussion in the literature about its epidemiology, pathogenesis, and characteristics in imaging exams. Given this scenario, this study aims to report the case of a patient diagnosed with xanthomatous meningioma and operated on at the Hospital da Restauração in Pernambuco, and to conduct a systematic review on the subject.

MATERIAL and METHODS

Research Question and Study Eligibility Criteria

The guiding question in the production of this study was, "What are the epidemiological characteristics of xanthomatous meningiomas?" Based on this, the inclusion and exclusion criteria for this study were defined.

We included case reports or case series on xanthomatous meningioma that detailed epidemiological information on the patient's sex and age and the tumor's location. Studies that did not report age and sex data were excluded.

Case Report and Immunohistochemical Diagnostic

The patient's information was taken from the physical and digital medical records, and for the immunohistochemical diagnosis of the tumor, the criteria of the latest WHO classification of central nervous system tumors were used.

Literature Search

Two researchers searched the PubMed and Mendeley databases using the terms "xanthomatous meningioma" and found a total of 56 articles.

Study Selection

The identification and screening of eligible studies for this research were carried out independently by two researchers, and there was no disagreement about the studies selected. The process of selecting, excluding, and screening the studies is detailed in Figure 1.

Data Collection

In the studies that were considered eligible for this work, the patient's gender and age, admission symptoms, tumor location, and tumor sign on MRI; [PS1] whether or not there was a recurrence; if there was a recurrence, how long after the resection surgery; and the immunohistochemical markers of meningothelial cells and foamy cells were collected. This information can be seen in more detail in Table I.

Ethics and Consent Statement

The studies involving human participants were reviewed and approved by the Ethics and Research Committee of the Hospital da Restauração de Pernambuco, which is affiliated with CONEP (National Commission for Ethics in Research), which is part of the Brazilian government's Department of Health. The patient was informed and provided written informed consent to the anonymous publication of her case (reference number of the hospital's ethics committee: 5198).

Statistical Analysis

As this was a descriptive study in which only nominal qualitative variables and quantitative variables were analyzed, the statistical tests used were percentage, mean, and standard deviation. SPSS software was used to carry out these tests and data management.

RESULTS

In this article, we carried out a systematic review of xanthomatous meningiomas and reported the case of a patient with xanthomatous meningioma who underwent surgery at the Hospital da Restauração in Pernambuco.

Case Report

The 44-year-old female patient was admitted to the hospital's emergency department with disorientation which, according to her relatives, had started hours before she was seen. It was also reported that she complained of a chronic headache.

On physical examination, the patient did not show any alterations in motor function or sensitivity; however, due to her disorientation and headache, a CT scan of her skull was requested, which revealed the presence of an isodense mass in the left frontal region. After this, an MRI scan was carried out and revealed a heterogeneous contrast uptake lesion that was isointense on T1 and T2 (Figure 2). Then, surgery was scheduled and took place without any intraoperative or postoperative complications.

At the last follow-up, 13 months later, the patient had no alterations on physical examination, and the last MRI showed no signs of recurrence.

Over the course of 10 years, a total of 580 patients with meningioma were operated at the hospital, and there was only one patient diagnosed with xanthomatous meningioma. Despite the bias of this result being related to a single center, it is

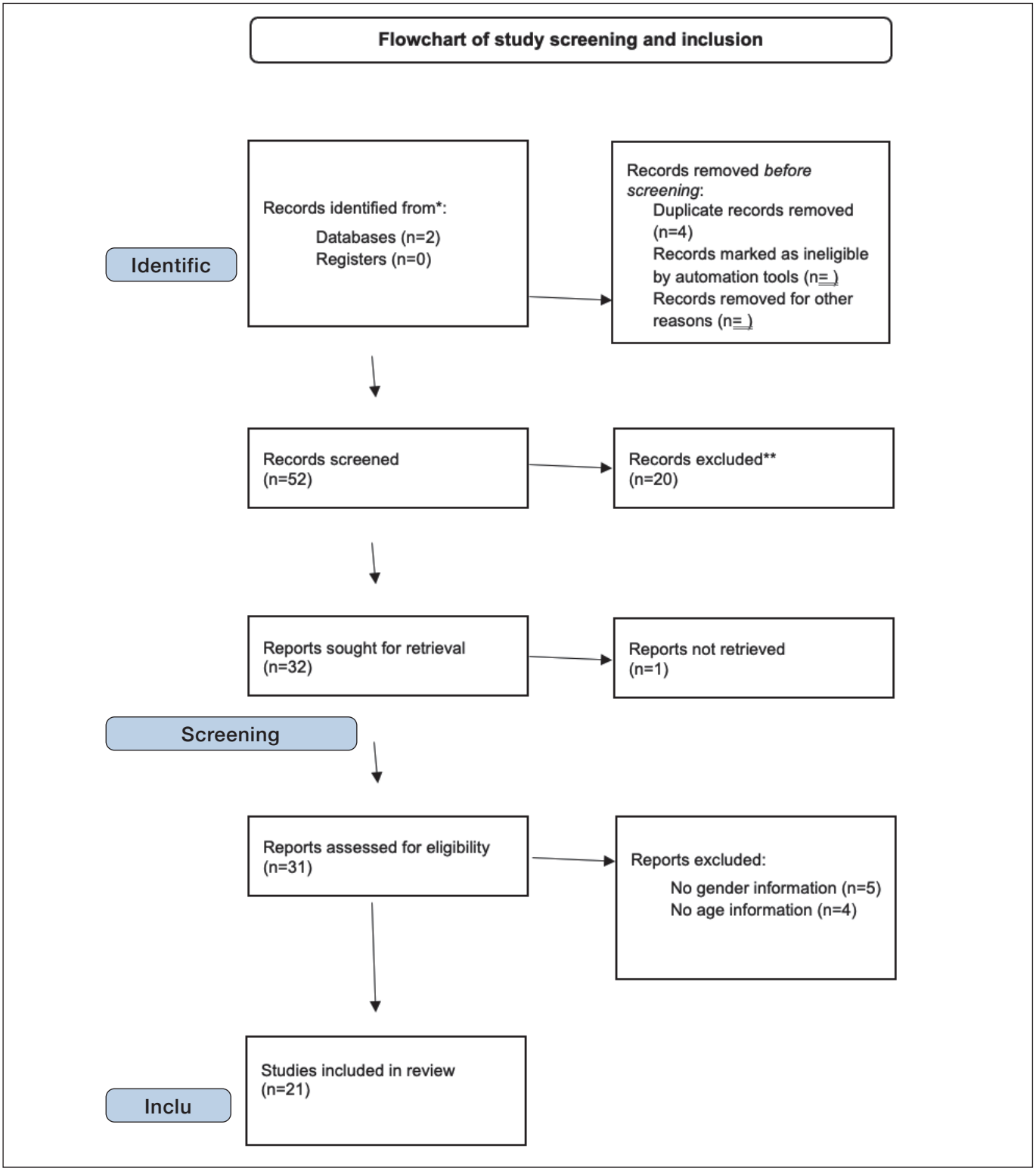

Figure 1: Flowchart of study screening and inclusion.

Table I: Patient Characteristics

Study	Sex	Age (years)	Location	Clinical symptom	Recurrence	Follow up (months)	Meningothelial cells markers	Xanthomatous cells markers
Yamashita et al. (1981), (36)	Male	51	Frontal	Seizures	Not informed	Not informed	Not informed	Not informed
Fujii et al. (1988), (6)	Male	74	Frontal	Cognitive deficit	Not informed	Not informed	Not informed	Not informed
Maehara et al. (1990), (18)	Female	48	Temporal	Seizures Motor deficit	Not informed	Not informed	Not informed	Not informed
Katayama et al. (1993), (13)	Female	37	Frontal	Seizures	No	18	Not informed	Not informed
Kepes (1994), (14)	Male	24	Parietal	Seizures Motor deficit	Not informed	Not informed	Not informed	Not informed
Okamoto et al. (1996), (21)	Male	66	Tentorium	Palpebral ptosis	Not informed	Not informed	Not informed	Not informed
Germanò et al. (1996), (8)	Female	2	Posterior Fossa	Headache	No	2	EMA, Vimentin, S100 and CR3/43	Not informed
Ijiri et al. (2000), (9)	Male	10	Frontal	Not informed	No	24	Vimentin, CD68 and HAM56	Vimentin, CD68 and HAM56
Roncaroli et al. (2001), (26)	Female	58	Frontal	Headache	No	120	Vimentin	EMA
Roncaroli et al. (2001), (26)	Female	27	Petrous bone	Incidental	Not informed	Not informed	EMA	EMA
Roncaroli et al. (2001), (26)	Female	59	Frontal	Seizures	No	36	EMA	EMA
Roncaroli et al. (2001), (26)	Female	70	Temporal	Seizures	No	24	EMA	EMA
Roncaroli et al. (2001), (26)	Male	79	Occipital	Gait instability	Not informed	Not informed	EMA	EMA
Ikota and Nakazato (2008), (10)	Female	61	Parietal	Headache	No	Not informed	EMA, vimentin and FA	CD68, MAC387, lysozyme, AAT, AACT and FA
Ishida et al. (2013), (11)	Male	76	Frontal	Dizziness	Not informed	Not informed	EMA, vimentin and adipophilin	EMA, vimentin, CD68, lysozyme, MAC387, adipophilin
Tang et al. (2013), (30)	Male	22	Frontal	Headache	Not informed	Not informed	EMA and vimentin	Not informed
Tang et al. (2013), (30)	Male	68	Frontal	Diplopia	No	Not informed	EMA, vimentin and GFAP	Not mentioned
Chougule et al. (2015), (3)	Female	24	Temporal and Parietal	Headache and visual deficits	Not informed	Not informed	EMA	EMA
Ersoz et al. (2019), (5)	Male	32	Frontal	Dizziness and tinnitus	No	8	EMA, vimentin and PR	EMA, CD68 and adipophilin

Table I: Cont.

Study	Sex	Age (years)	Location	Clinical symptom	Recurrence	Follow up (months)	Meningothelial cells markers	Xanthomatous cells markers
Wong et al. (2018), (35)	Female	83	Frontal	Motor deficit	No	3	EMA, vimentin, PR and S100	EMA, vimentin, CD68, PR, S100 and CD11
Kim et al. (2020), (15)	Female	27	Frontal	Not informed	Not informed	Not informed	Not informed	Not informed
Kim et al. (2020), (15)	Female	61	Frontal	Not informed	Not informed	Not informed	Not informed	Not informed
Saygin et al. (2021), (27)	Male	59	Frontal	Headache	Yes	84	EMA, vimentin, SSTR2 and PR	EMA, CD68, CD163, lysozyme and adipophilin
Joseph et al. (2021), (12)	Male	44	Parietal	Motor deficit	Not informed	Not informed	EMA	EMA and CD68
Patil et al. (2021), (23)	Female	43	Temporal	Not informed	Not informed	Not informed	EMA	EMA and CD68
Baishya et al. (2021), (2)	Female	62	Frontal	Motor deficit	Not informed	Not informed	EMA	EMA and CD68
Altindag et al. (2022), (1)	Female	40	Parietal	Headache	No	48	EMA, Vimentin and PR	EMA, Vimentin, PR CD68 and lysozyme
Present study. (2024)	Female	44	Frontal	Cognitive deficit	No	13	EMA and vimentin	EMA and vimentin

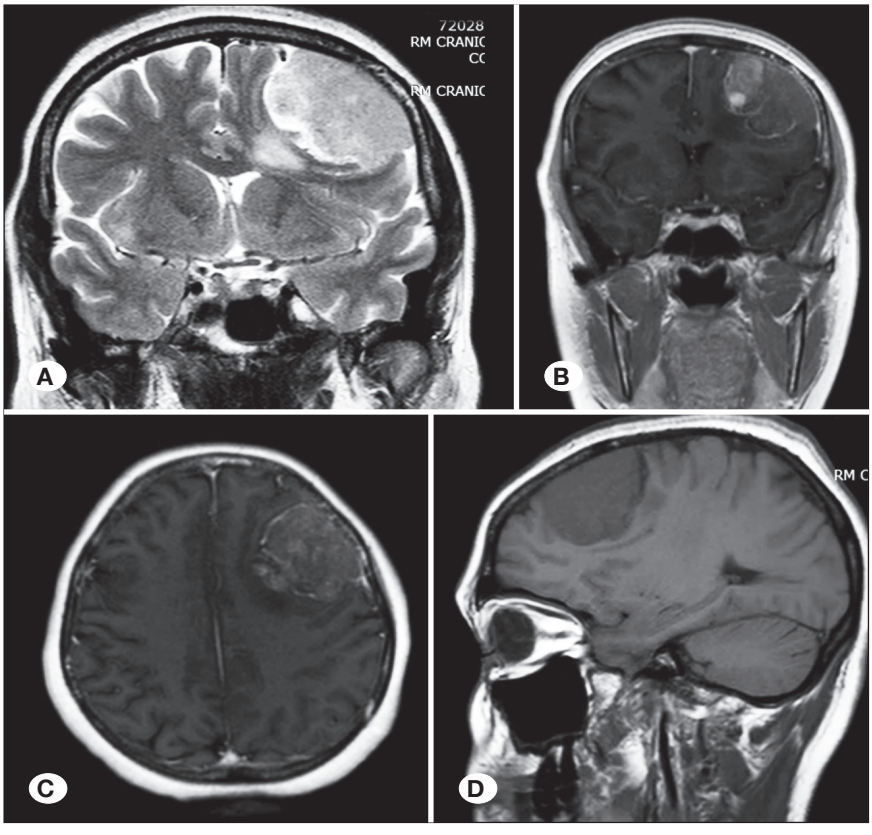

Figure 2: Preoperative magnetic resonance imagings (MRIs). **A)** Coronal T2-weighted MRI showing an isointense lesion. **B)** Coronal post contrast-enhanced T1-weighted MRI showing an heterogeneous contrast uptake. **C)** Axial post contrast-enhanced T1-weighted image. **D)** Sagittal T1 -weighted MRI showing an isointense lesion.

possible to estimate that xanthomatous meningiomas correspond to 0.17% of meningioma cases.

Written informed consents were obtained from the individuals (and/or legal representatives) for the publication of the cases.

Patient Characteristics

The systematic review included 21 studies and 27 patients, which together with this study's report made a total of 28 individuals.

Of all 28 patients, 16 (57.1%) were female and 12 (52.9%) were male, which represents a ratio of 1.33 women to 1 man. These individuals' average age was 48.2 years (n=28; range, 2-83 years; SD, 21.5).

In terms of location, 16 tumors were found in the frontal region (57.2%), 4 (14.3%) in the parietal region, 4 (14.3%) in the temporal region, 2 in the occipital region (7.2%), 1 in the temporal-parietal region (3.5%), and 1 in the posterior fossa (3.5%) (Table I).

The main symptoms that led these patients to seek medical help were headache in 6 patients (21.4%), followed by seizures in 4 patients (14.2%), motor deficits in 3 (10.8%), cognitive deficits in 2 (7.1%), seizures and motor deficits in 2 (7.1%), palpebral ptosis in 1 (3.6%), incidental in 1 (3.6%), headache and visual deficits in 1 (3.6%), dizziness and tinnitus in 1 (3.6%), dizziness in 1 (3.6%), diplopia in 1 (3.6%), and gait instability in 1 (3.6%); in 4, the information is missing (14.2%) (Table I).

Among the 28 patients, information on recurrence was only available for 13. The average follow-up time was 34.5 months (n=13; range, 2-120 months; SD, 36.9), and only 1 of the patients had a recurrence, which happened at 84 months (Table I).

MRI Characteristics

Information on MRI findings was available in 13 patients. In the T1 sequence, 5 (38.4%) were isointense, 1 (7.7%) hypointense, and 1 (7.7%) heterogeneous with isointense and hyperintense areas, while 6 (46.2%) were missing this information. In T2, 2 (15.3%) were isointense, 1 (7.7%) was hyperintense, and 1 (7.7%) was heterogeneous with isointense and hyperintense areas, while in 9 (69.4%), no information was available (Table II).

Regarding contrast uptake in these tumors, as assessed by MRI, 6 (46.2%) had homogeneous contrast uptake, 4 (30.8%) had a heterogeneous contrast uptake pattern, 2 (15.3%) had no contrast uptake, and this information was not available for 1 (7.7%) patient (Table II).

Immunohistochemical Characteristics

With regard to immunohistochemical markers, we collected markers from the meningothelial cell regions, which were available in 21 cases, and foamy cells, which were available in 18 cases.

The meningothelial cells were positive for epithelial membrane antigen (EMA) in 19 (90.4%) of the cases and negative for CD68 in 20 (95.2%). The foamy cells were positive for EMA in 15 cases (78%), for CD68 in 10 cases (52%), and for lysozyme in 4 cases (21%). In 8 cases (42%), the foamy cells were positive for EMA and CD68 simultaneously.

It's important to note that not all the studies carried out immunohistochemical analysis with the CD68 and lysozyme

Table II: Magnetic Resonance Imaging Characteristics of Xanthomatous Meningiomas

Study	T1 weighted	T1 post-gd	T2 weighted
Yamashita et al. (1981), (36)	Not mentioned	Heterogeneous contrast uptake	Not mentioned
Fujii et al. (1988), (6)	Not mentioned	No contrast uptake	Not mentioned
Maehara et al. (1990), (18)	Not mentioned	Homogeneous contrast uptake	Not mentioned
Katayama et al. (1993), (13)	Hyperintense and isointense areas	Not mentioned	Not mentioned
Okamoto et al. (1996), (21)	Isointense	Homogeneous contrast uptake	Not mentioned
Ikota and Nakazato (2008), (10)	Not mentioned	Homogeneous contrast uptake	Not mentioned
Ishida et al. (2013), (11)	Not mentioned	Homogeneous contrast uptake	Not mentioned
Ersoz et al. (2019), (5)	Isointense	No contrast uptake	Hyperintense and isointense areas
Wong et al. (2018), (35)	Not mentioned	Heterogeneous contrast uptake	Not mentioned
Patil et al. (2021), (23)	Hypointense	Homogeneous contrast uptake	Isointense
Saygin et al. (2021), (27)	Isointense	Heterogeneous contrast uptake	Hyperintense
Joseph et al. (2021), (12)	Isointense	Homogeneous contrast uptake	Not mentioned
Present study. (2024)	Isointense	Heterogeneous contrast uptake	Isointense

markers, so the actual proportion of tumors positive for these markers may be higher than reported.

DISCUSSION

Epidemiology Xanthomatous Meningiomas

It is known that meningiomas have a higher incidence among women, with some references estimating a ratio of 3.28 women to 1 man between the ages of 35-44. However, for xanthomatous meningiomas, the results showed, despite the low sample size, an incidence of 1.33 women to 1 man, which represents a smaller gap between the proportion of men and women when compared to meningiomas in general (30).

Regarding age, the average age of patients with xanthomatous meningioma at diagnosis was 48.5 years, about 17 years below the average for meningiomas in general, which is 65 years (21).

As with meningiomas in general, xanthomatous meningiomas have been shown to have a good prognosis with surgical resection, with only 1 (7.6%) case of recurrence among the 13 in which this information was available.

Cellular Origins of Xanthomatous Meningiomas

The existence of xanthomatous meningiomas has been recognized for some time, but only about 20 studies, primarily case reports and series, have been conducted on this rare tumor. Histologically, it is characterized by meningothelial tumor cells and lipid-filled xanthomatous cells (14).

The origin of these cells is debated: some propose they arise from macrophages migrating to the tumor, supported by CD38 expression, while others suggest they are degenerated meningothelial cells accumulating lipids due to low blood supply (10,24,27). Supporting the latter, 78% of reported cases show EMA positivity in xanthomatous cells, and electron microscopy reveals features such as interdigitations, desmosomes and hemidesmosomes typical of meningothelial cells (26).

Differential Diagnoses of Xanthomatous Meningiomas

When making the histopathological and immunohistochemical diagnosis of xanthomatous meningiomas, it is important to consider possible differential diagnoses, since, unlike other pathologies with which it can be confused, such as clear cell meningioma, it has a good prognosis.

Lipomatous meningiomas are a subtype of metaplastic meningiomas, typically grade I, where cells accumulate lipids resembling mature adipocytes and stain with the S100 marker, unlike xanthomatous meningiomas. Some meningiomas may show both xanthomatous and lipomatous features as was reported in the case series by Roncaroli et al. (4,7,26,28).

Microcystic meningiomas, with cytoplasmic vacuoles and extracellular fluid, may appear similar to xanthomatous meningiomas but lack CD68 expression and have cells with long cytoplasmic processes, something unusual in xanthomatous meningioma (12,27).

Unlike the other differential diagnoses mentioned above clear cell meningiomas, although appearing benign, have a worse prognosis and can be differentiated by their glycogen-rich cytoplasm, large amounts of collagen in the stroma, and because they are stained with periodic acid-Schiff (PAS) (5,27). Although rare, xanthomatous changes can also occur in anaplastic and atypical meningiomas, as reported by Taraszewska A et al. (31).

Histiocytic meningiomas present significant histiocytic infiltration and constitute a rare subtype that can cause diagnostic confusion. According to Liu et al. (16), histiocytes in these situations commonly express EMA, CD68, and CD4.

Because Rosai-Dorfman disease (RDD) may present as a dural mass, it can be confused with a xanthomatous meningioma. However, emperipolesis, a pathognomonic finding, and polymorphic infiltration of histiocytes, lymphocytes, and plasma cells are characteristics of RDD. Moreover, RDD histiocytes' non-meningeal origin is supported by the lack of EMA expression in these cells (16).

Imaging Features of Xanthomatous Meningiomas

Katayama et al. described 5 cases of xanthomatous meningiomas as hypodense masses on CT scans, a characteristic that differs from the majority of meningiomas, which are usually hyperdense or isodense masses. In the case described in this article, the patient's lesion appeared isodense to the parenchyma on the CT scan of the skull (13,17).

Regarding these tumors' appearance tumors on MRI, in theory, they should be hyperintense on T1 and T2 weighting due to the lipid content present; however, of the 13 cases, including the one reported in this study, in which descriptions of this neoplasm's imaging characteristics were found, on T1 and T2 weighting, only 1 and 2 tumors, respectively, appear as hyperintense lesions. One possible explanation for this is the bias due to the limited number of studies reporting the radiological characteristics of xanthomatous meningiomas.

Normally, meningiomas show homogeneous contrast uptake; in this study, 46.2% of the tumors behaved in this way. However, meningiomas can also have heterogeneous contrast uptake, a characteristic seen in 30.8% of the tumors in this study, due to the presence of calcification, cysts, or necrosis, and it was not possible to establish a difference in these aspects between xanthomatous meningiomas and other types of meningioma (33,35).

Limitations

It should be noted that this study has some limitations. The small sample size due to the rarity of xanthomatous meningiomas limited the ability to make broad epidemiological and clinical generalizations. Furthermore, although useful, imaging findings still need more research to elucidate their function in identifying and distinguishing xanthomatous meningiomas from other subtypes of meningiomas.

CONCLUSION

This study on xanthomatous meningiomas, through a systematic review and case presentation, offers valuable insights into this rare neoplasm. The results underscore the complexity and uniqueness of this type of tumor, highlighting the importance of immunohistochemical examination in characterizing the neoplasm and epidemiological differences between xanthomatous meningiomas and meningiomas in general. Despite its intrinsic limitations, this study makes a significant contribution to understanding this entity, highlighting the urgent need for more publications on this pathology's characteristics, especially the radiological features, in order to improve diagnostic accuracy and guide surgical planning.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: PLNG, ICSS, MGFA
Data collection: PLNG, ICSS
Analysis and interpretation of results: PLNG, ICSS, AAPL
Draft manuscript preparation: PLNG, ICSS, AAPL
Critical revision of the article: LEAS, IVF, ABCJ
All authors (PLNG, ICSS, MGFA, AAPL, LEAS, ABCJ, IVF) reviewed the results and approved the final version of the manuscript.

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