

Asymptomatic and symptomatic glial cysts of the pineal gland

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Abstract

Glial cysts of the pineal gland are benign and mostly asymptomatic incidental lesions found in the brain MRI or at autopsy examinations. In rare cases pineal cysts become symptomatic and require surgical intervention. Symptomatic glial cysts may be clinically and radiologically indistinguishable from cystic neoplasms of the pineal region; therefore, histopathological diagnosis is critical for further prognosis and therapy in operated patients.

In this paper we present detailed histopathological characteristics of symptomatic glial cysts in 2 surgical cases and of asymptomatic cysts of the pineal gland found at random in 3 autopsy cases. Both surgical patients, a 19-year-old girl and a 17-year-old boy, presented with severe headaches, associated with syncope in one case and insomnia in the second one. Preoperative MR imaging suggested tumour of the pineal gland in case no. 2. Histopathological and immunohistochemical examination of the specimens from both surgical and all autopsy cases revealed a characteristic pattern of cystic structures within the pineal gland, surrounded by layers of a dense fibrillar glial tissue and pineal parenchyma, consistent with non-neoplastic glial cysts. Although histopathological findings in asymptomatic and symptomatic cysts are essentially the same, the cyst in surgical case 1 was unilocular and partly lined with ependymal cells, whereas the cysts in other cases were multilocular, comprising cavities of various size, formed in the central part of gliotic tissue or directly within the pineal parenchyma, and lacked ependymal lining. Possible pathophysiological and clinicopathological significance of some morphological variants of pineal glial cysts is discussed.

Key words: pineal gland, asymptomatic pineal cyst, symptomatic glial cyst.

Introduction

Non-neoplastic glial cysts of the pineal gland are relatively common incidental findings in brain MRI [4,12,14,19,33,34,36] or in autopsy studies [10]. Usually they have no clinical implications and remain asymptomatic for years. In analysed series of MRI

the occurrence of asymptomatic intrapineal cysts ranged between 0.2% [14] and 10.8% [12] of healthy volunteers and between 1.26% [33] and 4.3% [19] of patients examined for various neurological reasons. Most previous MRI studies revealed pineal cysts with a size of no less than 5 mm in diameter [4,19,36]. With the improved MRI techniques a higher inciden-

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ce of pineal cysts has been reported including smaller cystic changes, even with measurements of 2 mm [12]. Recently, the use of high-resolution MR imaging demonstrated that 23% of volunteers had pineal cysts with a mean diameter of 4.3 mm (range 2-14 mm) and 13% demonstrated smaller cystic changes with the largest diameter less than 2 mm [34]. The proportion of pineal cysts and pineal small cystic lesions observed by Pu et al. [34] in an MRI study was consistent with previous results of a post-mortem study reported by Hasegawa et al. [10]. These authors found that cysts larger than 2 mm in diameter were seen macroscopically in 34% of pineal glands, whereas microscopically recognizable cystic changes, less than 2 mm in diameter, occurred in 28% of pineal glands.

In contrast to asymptomatic cystic lesions of the pineal gland, symptomatic glial cysts are rare and could require surgical intervention. Enlarged glial cysts with a size of at least 15 mm in diameter are related to clinical syndromes referable to a mass lesion [6,13,22]. The most common symptoms, resulting from compression of the surrounding structures, particularly the quadrigeminal plate and cerebral aqueduct, include headaches of variable intensity, visual and oculomotor disturbances and obstructive hydrocephalus [6,15,25,26,30,41]. Less frequently patients present with ataxia [6,41], motor and sensory impairment [6,15,25,30] or mental and emotional disturbances [15,37]. Sudden death due to a cystic lesion of the pineal gland has also been reported [27,35].

The diagnosis of pineal cyst is usually established by MRI; however, neuroradiological analysis without histological verification does not predict the benign glial nature of the lesion. Often, both clinical and radiological manifestations of symptomatic glial cysts may be indistinguishable from neoplastic pineal cystic lesions [6,8,37]. Therefore, histopathological study is definitive for critical diagnosis, further prognosis and therapy in patients operated on for pineal cystic lesion [5].

Glial cysts of the pineal gland are a relatively rare finding in routine biopsy material [2,5,16]. A cyst with typical morphology can be diagnosed easily, but occasionally the histopathological pattern can be confused with pineal parenchymal or astrocytic tumour, especially if fragmentary surgical specimens are obtained for microscopic examination [5,15]. Klein and Rubinstein [15] indicated that they are histologically most often mistaken for a pineocytoma. In their se-

ries of 7 cases of symptomatic glial cysts, referred for histopathological consultation, the initial diagnosis was pineocytoma in 4 cases. Similar observation of frequent misdiagnosis of pineocytoma in cases with glial cysts was obtained by one of the authors (E.M.), reviewing histopathological material from patients operated on in various neurosurgical centres.

In this paper we demonstrate morphological variants of pineal glial cyst that may cause both radiological and histopathological pitfalls. Detailed histopathological features of glial cysts were documented in 2 surgical cases of symptomatic cyst of the pineal gland and in 3 autopsy findings of asymptomatic pineal cysts. Clinical and radiological manifestations of symptomatic glial cysts in presented cases are discussed.

Material and Methods

A histopathological study was performed on surgical specimens obtained from 2 cases of symptomatic pineal cysts and on 3 cystic pineal glands taken at random from non-selected autopsy cases. Formalin-fixed material was routinely processed for paraffin and the sections were stained with haematoxylin and eosin (H&E). Immunohistochemical staining was performed with primary antibodies against glial fibrillar acidic protein (GFAP), neurofilament proteins (NFP) and synaptophysin, using the streptavidin-biotin-peroxidase complex method (all reagents provided from Dako).

Report of cases

Biopsy cases 1-2

Case 1. An 18-year-old girl presented with a history of severe headache not responding to medical treatment. Headache was accompanied by nausea and vertigo and for 2 months by syncope. The symptoms began after contusion of the brain that she had undergone in a road accident 2 years ago. Since then she had been treated with Lamitrin because of suspicion of epilepsy. At admission, neurological examination and routine laboratory tests were normal. MRI of the brain revealed a round cyst measuring 14 mm in diameter in the pineal gland region (Fig. 1A). The cyst compressed and modulated the quadrigeminal plate without signs of cerebral aqueduct obstruction. Size of the ventricular system was normal. Preope-

rative diagnosis was pineal cyst. Total resection of the cyst was accomplished by occipital-transtentorial approach. Postoperatively, the patient experienced a gradually resolving Parinaud's symptom, not present before surgery. Frequency and intensity of headache were significantly diminished. In the control MRI obtained 6 months after cyst resection the deformation of the quadrigeminal plate was partially reduced (Fig. 1B). The patient was free of severe headache.

For the histopathological study small fragments of the cyst wall were obtained. Microscopically, the cyst wall consisted of layers of dense fibrillar gliotic tissue, containing Rosenthal fibres and a narrow zone of pineal parenchyma (Fig. 2A-B). Some segments of the cyst wall disclosed ependymal cells lining the inner glial layer (Fig. 2C). The external surface of the wall was covered by a thin band of connective tissue. Immunostains showed strong reactivity of GFAP in glial layers (Fig. 3A) and in dispersed interstitial astrocytes within pineal parenchyma, whereas the pineocytes were immunopositive for NFP and synaptophysin (Fig. 3B).

Case 2. A 17-year-old boy suffered for months severe headache with insomnia and occasional vertigo. The first MRI examination of the brain, obtained 6 months ago, demonstrated a cystic mass of irregular outline in the region of the pineal gland, with dimensions of 14×16×11 mm. The lesion showed inhomogeneous contrast enhancement and suggested tumour of the pineal gland. At admission, MR imaging showed the same appearance of the lesion as previously (Fig. 4). Neurological examination and laboratory tests, including tests for alpha-fetoprotein, CEA and HCG, were normal. The lesion was totally resected by the infratentorial supracerebellar approach. Postoperative course was uneventful, but headache symptoms were maintained.

Histopathological study of surgical specimens revealed multilocular cysts surrounded by bands of fibrous glial tissue (Fig. 5A) or directly by pineal parenchyma. The cyst cavities demonstrated variable dimensions and protein fluid content in some smaller ones. Rosenthal fibres within glial tissue and deposits of calcification within pineal parenchyma

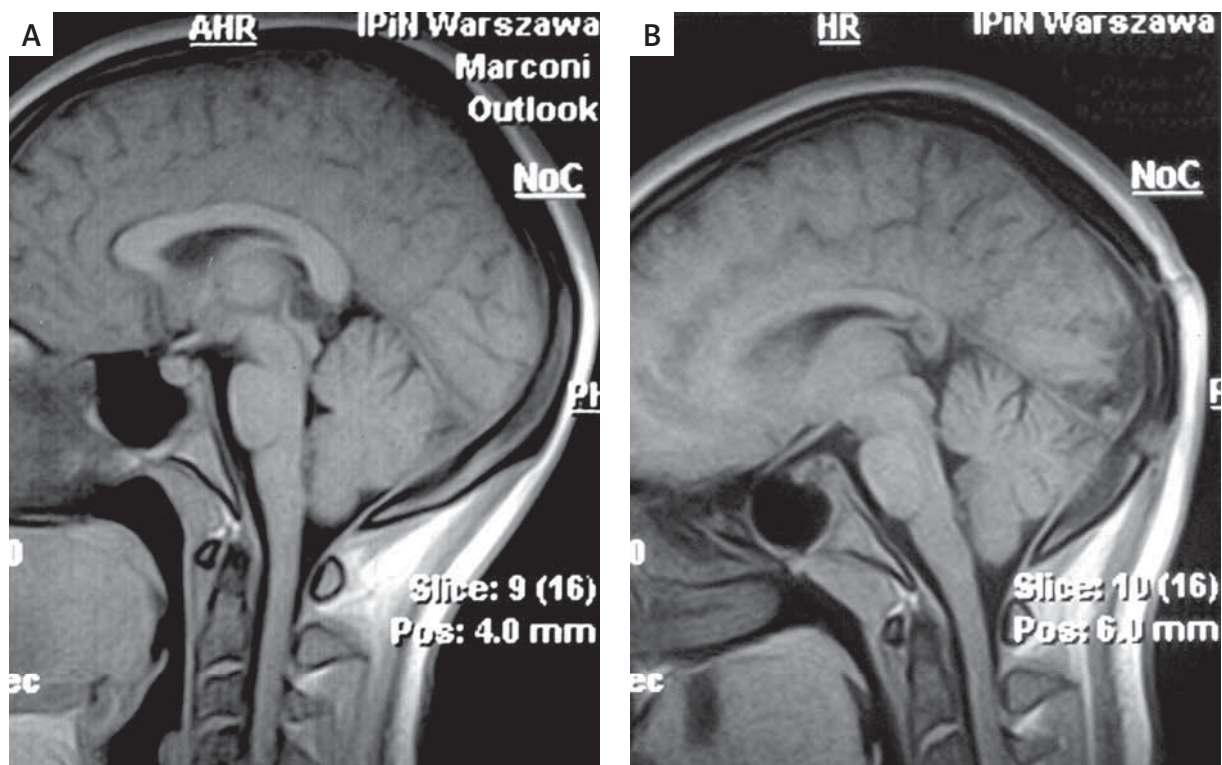


Fig. 1. Case 1. A. Preoperative MR sagittal image shows a round pineal cyst with thin wall and compression effect on quadrigeminal plate; B. Postoperative MR sagittal image shows total removal of the cyst

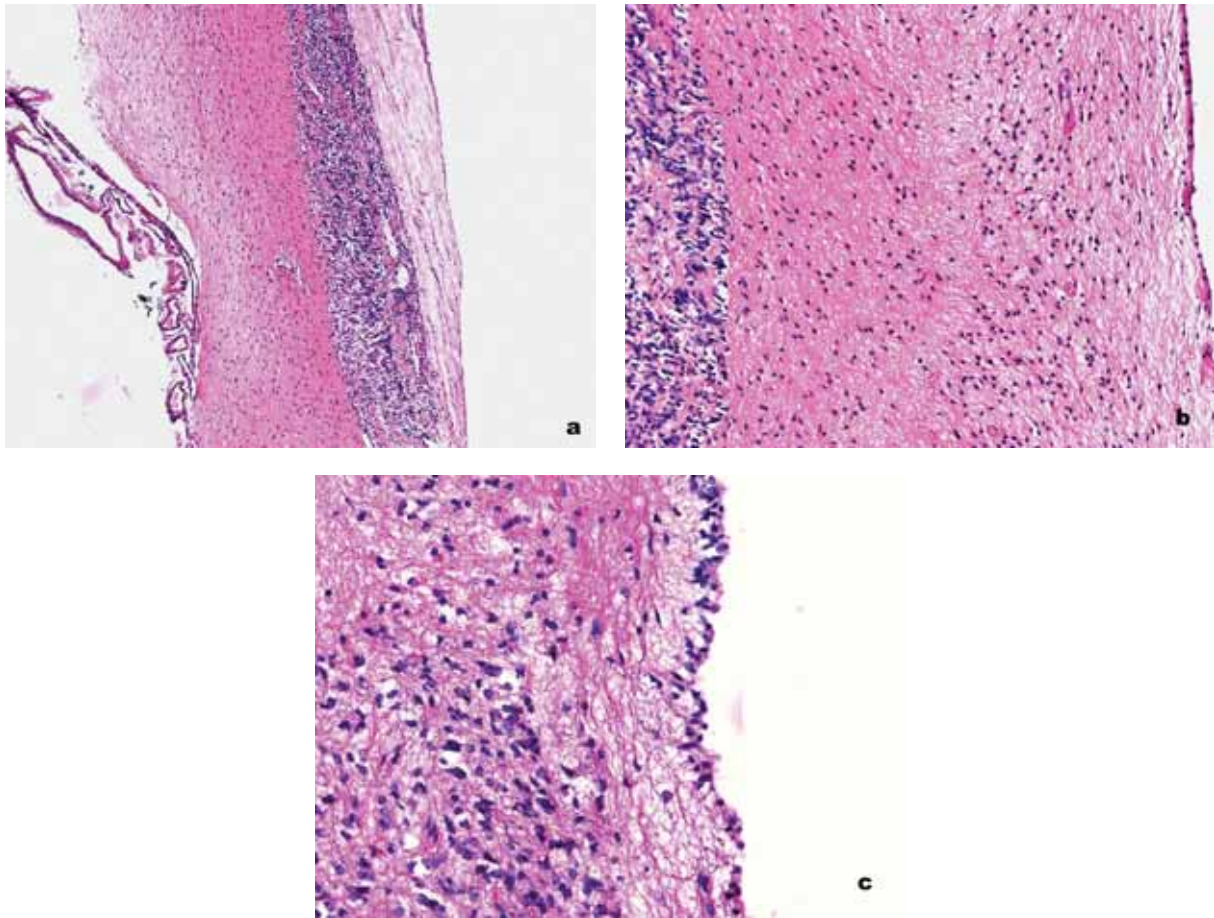


Fig. 2. Case 1. A. Layered structure of cyst wall composed of fibrillar glial tissue, pineal parenchyma and external connective tissue covering. HE. $\times 100$; B. Fragment of inner layer of cyst wall exhibiting densely fibrillar glial tissue, in part lined by flat cells. HE. $\times 200$; C. Ependymal cell lining of inner glial layer of cyst wall. HE. $\times 400$

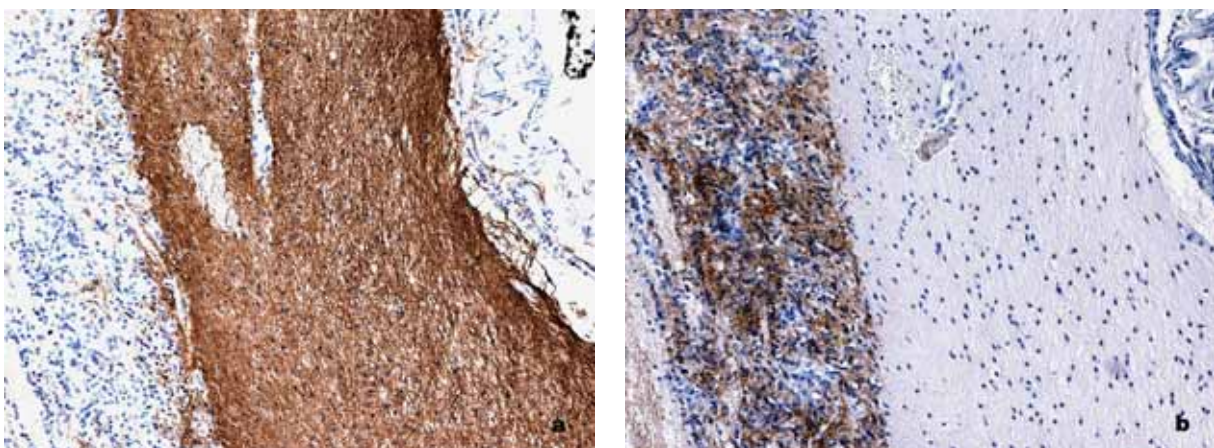


Fig. 3. Case 1. A. Strong GFAP reactivity in the layer of glial tissue. $\times 200$; B. Positive staining for synaptophysin in the pineal parenchyma layer. $\times 200$

were observed (Fig. 5B). In immunohistochemistry, the layers of glial tissue showed strong reactivity for GFAP (Fig. 6A), whereas pineal parenchyma was stained with synaptophysin and NFP (Fig. 6B).

Autopsy cases 3-5

Case 3. A 69-year-old man, without history of disease, died suddenly because of rupture of the aor-

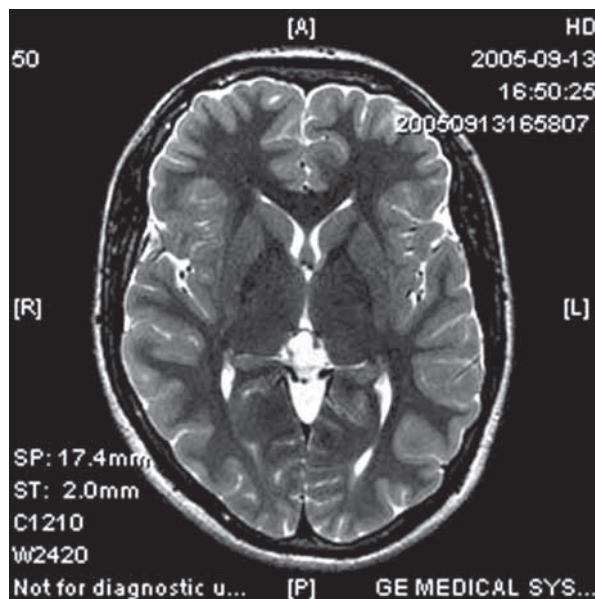


Fig. 4. Case 2. T2-weighted MR axial image shows irregular cystic mass lesion in the region of the pineal gland. Ventricular system is normal

ta aneurysm. Autopsy study of the brain revealed a round tumour of 13 mm in diameter, which was loosely attached with leptomeninges of the brain stem and resembled meningioma. On cross-section it was greyish and cystic. Microscopic examination of the tumour revealed a cystic body of the pineal gland, with a large cyst of 7 mm in diameter surrounded by a vast layer of fibrous glial tissue (Fig. 7A). In the adjacent pineal parenchyma numerous interstitial astrocytes and small areas of fibrillar gliosis with Rosenthal fibres were seen (Fig. 7B). The diagnosis was glial cyst of the pineal gland.

Case 4. A 34-year-old woman died because of post-alcoholic hepatic insufficiency.

At autopsy study, the brain was macroscopically unchanged. The pineal gland with size of 8 mm in diameter was multicystic in appearance on cross-section. Microscopically, there were several areas of gliotic tissue, exhibiting signs of cystic degeneration and formation of small cavities in the centre of some ones within the pineal parenchyma (Fig. 8A-B). Lobular arrangement of pineal cells was seen.

Case 5. A 66-year-old man died because of circulatory insufficiency. At autopsy study old postapoplectic foci were found in the brain. The pineal gland with diameter of 9 mm was multicystic in cross-section with the central cyst measuring 4 mm in the largest dimension. Microscopically there were multilocular cysts, in parts surrounded by glial fibrillar layers (Fig. 9A) or directly by bands of pineal parenchyma, separating smaller cavities (Fig. 9B). Pineal parenchyma

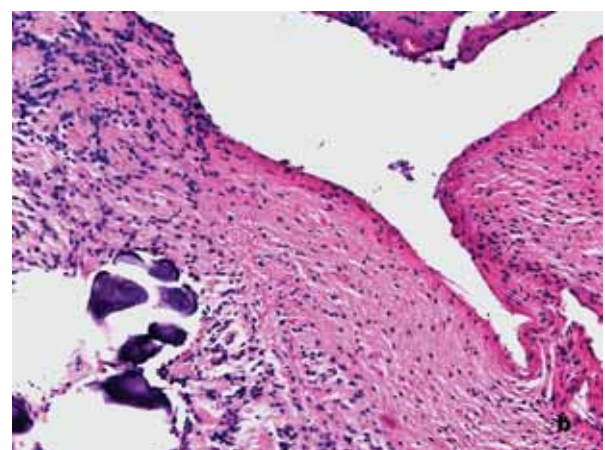
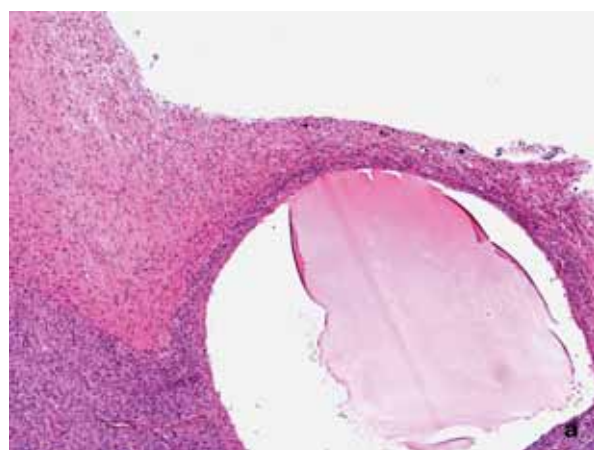


Fig. 5. Case 2. A. Multilocular cyst with cavities of variable dimensions, with proteinaceous fluid content in one smaller cavity. Cavities are surrounded by fibrous glial tissue bordering with pineal parenchyma. HE. x100; B. Rosenthal fibres in inner glial layer of cyst wall and calcification deposits in neighbouring pineal parenchyma are seen. HE. x200

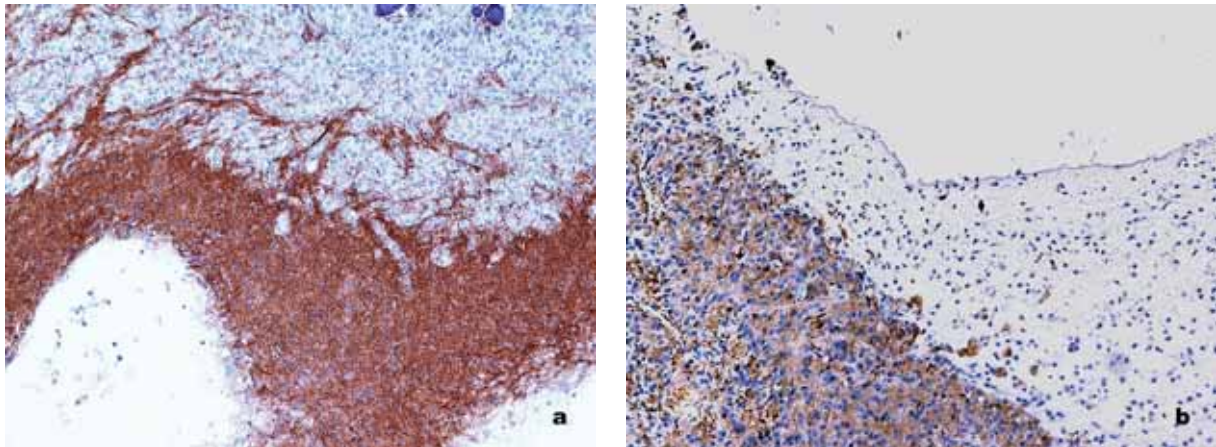


Fig. 6. Case 2. A. Cyst wall with strong GFAP immunostaining of densely fibrillar glial layer and scattered interstitial astroglia within pineal parenchyma layer. $\times 200$; B. NFP positive immunostaining in pineal parenchyma and negative in glial layer of cyst wall. $\times 200$

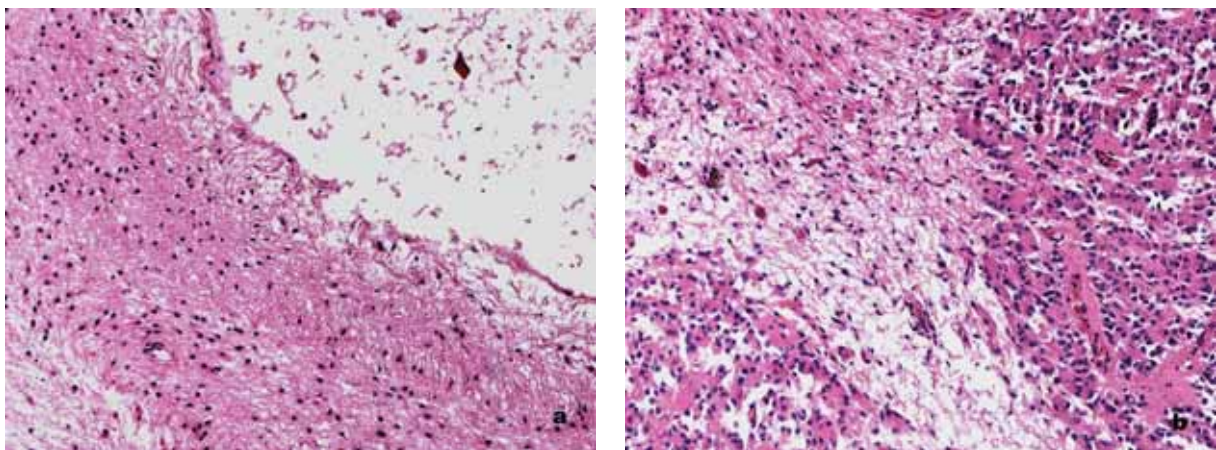


Fig. 7. Case 3. A. Inner glial layer of cyst wall. HE. $\times 200$; B. Focal fibrous gliosis with Rosenthal fibres within pineal parenchyma. HE. $\times 200$

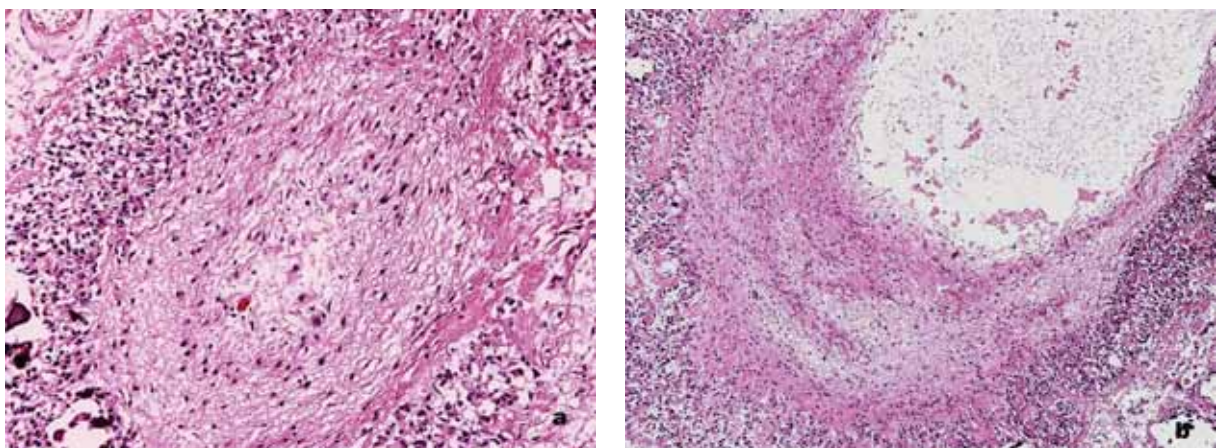


Fig. 8. Case 4. A. Gliotic plaque with Rosenthal fibres in parenchyma of pineal gland. HE. $\times 200$; B. Small cyst formed within a gliotic plaque. HE. $\times 100$

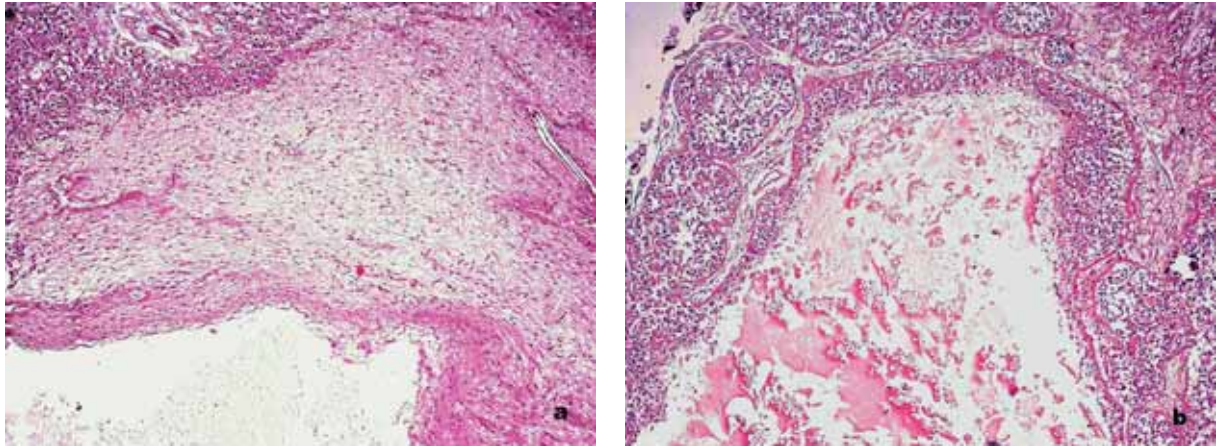


Fig. 9. Case 5. A. Vast layer of fibrillar, partly spongy glial tissue surrounding large cavity of multilocular cyst. HE. $\times 100$; B. Cavity of the cyst surrounded by pineal parenchyma with evident lobular architecture. HE. $\times 100$

showed lobular architecture and obvious interstitial gliosis.

Discussion

Glial cysts without known clinical implications may exist in 23% [34] to about 40% of the human pineal gland in adults [10], but the natural history of cyst development and the risk of its subsequent enlargement and clinical manifestation are not well understood [1].

Generally, it is assumed that mechanisms responsible for pineal glial cyst formation include dysontogenic and degenerative phenomena [6,11,23]. The pineal gland develops by the proliferation of walls of the third ventricle diverticulum in the diencephalic roof. A remnant of the pineal diverticulum or distension of its obliterated portion has been postulated as a possible source of pineal cysts [36,39]. Particularly, this mechanism could be taken into consideration in glial cysts exhibiting ependymal cell lining, like the cyst in the reported case 1. However, ependymal lining was not present in case 2 or in the asymptomatic cysts from autopsy cases, in which degenerative origin of pineal cyst formation could be suggested. In these cases the cysts of variable dimensions were surrounded either by fibrous glial tissue or directly by pineal parenchyma, containing an admixture of prominent interstitial gliosis. It has been stated that degeneration of pineal parenchyma leads to increased astrocytic proliferation, in particular to hyper-

plasia of interstitial astroglial fibres [11]. However, no specific causes have been correlated with these abnormalities. Morphological studies of pineal glands have evidenced focal gliosis or gliotic plaques with central cystic degeneration in patients who died from various diseases at different ages [31,40]. Pineal cysts adjacent to gliotic plaques were also demonstrated in newborns and young infants at autopsy study, suggesting that many of them may evolve from necrotic and hemorrhagic changes found in the fetal pineal glands [17].

The processes causing an asymptomatic pineal cyst to become symptomatic are unclear and occur infrequently [1]. Follow-up MR imaging of the asymptomatic cysts demonstrated that their size remained stable after months or years [1,4,9,34,37]. In individual patients the cysts exhibited enlargement [1,6] or involution [1,37], but small changes in their size were not associated with specific clinical symptoms [1].

A relationship between size of the cyst and appearance of the symptoms is generally postulated [2,23], but in many cases it may be irrelevant. Overlapping dimensions of the asymptomatic and symptomatic cysts, especially within the range of the cyst diameter from 10 to 20 mm, have frequently been observed [25]. Symptomatic cysts vary in size from 7 mm to 4.5 cm in diameter [7,15], whereas asymptomatic cysts are usually less than 10 mm in diameter [19] but sometimes reach dimensions of 20 to 22 mm [1,33]. In rare instances, relatively small cysts with diameter of 12 to 14 mm are known to cause

sudden death due to intracystic bleeding and acute hydrocephalus [27,35]. Therefore, the appearance of clinical symptoms has been attributed to factors determining the rapid enlargement of a pineal cyst, such as intracystic bleeding [6,8,15,24,29], rapid coalescences of pre-existing smaller cavities [6,37], increase of the fluid pressure gradient between the third ventricle and cyst cavity [3] or direct inflow of CSF to the pineal cyst due to communication of the cyst with the third ventricle [13].

In our patient 1 contusion of the brain could be appreciated as the factor initiating enlargement of the pineal cyst, presumably via the mechanism of increased pressure of CSF within the third ventricle [3]. No evidence of recent or previous haemorrhage was found in our cases.

In this report both surgically treated patients presented with severe headaches. Moreover, a rare clinical presentation of syncope was noted in patient 2. In previous cases "pineal syncope" has been related to anterior-inferior movement of the cyst with subsequent aqueductal occlusion [41] or flexion at the waist [22].

Headaches are the most common and frequently the only symptom of pineal cysts in children [20] and in adults [6,25,26,39]. Several factors might be responsible for headaches, including disturbances of the CSF flow through the cerebral aqueduct [20], obstructive hydrocephalus and raised intracranial pressure [15,26], compression on the Galen vein and venous congestion [37]. On the other hand, in patients with otherwise normal neurological exam, the real relation between headache and the presence of a pineal cyst is not well established [32]. Pineal cysts prevail in women [4,7,9,34] and symptomatic cysts are most frequent in young women, at the age with also the highest frequency of migraine headache, suggesting the hypothesis of cyst formation dependent on hormonal influences in such condition as in the period of puberty or pregnancy [6,15,29,36,41].

It is assumed that asymptomatic cysts do not require treatment or follow-up study by MRI but a close clinical observation with indispensable neuroradiological control should be recommended [1,34].

In cases of symptomatic pineal cyst a common problem arises in interpretation of clinical and neuroimaging findings predicting indications or contra-indications for surgical procedures. Although it is still debated whether patients with symptomatic cysts should be followed or treated surgically, there is

agreement that surgical intervention should be undertaken in patients presenting hydrocephalus, progression of neurological symptoms or enlargement of the cyst [20,25,26,37,38]. The observation of Mander et al. [20] indicated that symptomatic pineal cysts in children should be followed up for many years and surgical treatment should be recommended only in a minority of cases.

Special importance for management prediction is preoperative discrimination of neoplastic cystic lesion from a non-neoplastic glial cyst. On MRI, the benign pineal cyst is typically rounded, unilocular, isointense or slightly hyperintense in relation to the CSF signal on T1-weighted and FLAIR images, with the wall thickness no more than 2 mm [5,7,8,15,19,37]. In contrast to usually unilocular, round or oval homogeneous cysts, a heterogeneous appearance of multilocular or multiseptate cysts with irregular enhancement often does not permit discrimination of benign and neoplastic cysts [5,8,19,28]. Especially, small cystic pineocytoma and glial pineal cysts showed similar MRI signal characteristics [5]. Nodular contrast enhancement and irregularities of the cyst wall, suggestive of pineocytoma, have been described in some glial cysts [8,28]. Also in our patient 2, the MRI examination resulted in no conclusive diagnosis of multilocular cystic lesion in the pineal gland region.

The importance of histopathological verification of such lesions for further prognosis and therapeutic concepts in operated patients was stressed by Engel et al. [5]. In their series of 13 patients with MRI diagnosis of pineal cysts histological diagnosis revealed 4 glial cysts, 6 pineocytomas, one low-grade astrocytoma, one arachnoid cyst and a teratoma.

When dealing with histopathological examination of pineal cystic lesions, special attention must be paid to obtaining adequate surgical specimens, permitting one to distinguish a glial cyst from pineal parenchymal or low-grade astrocytic neoplasms [2,5,25]. Sometimes, histological diagnosis of a glial cyst may cause serious problems, especially when fragmentary biopsy specimens lack the representative glial and pineal components of the cyst wall. Gross specimens regaining cystic shape by floating it intact and cutting perpendicular sections through the cyst wall should minimize the chance of misdiagnosis [2].

Typically, the cyst wall consists of three layers, namely glial, pineal and collagenous [5,6,15,22,25,28]. Small fragments of the cyst wall, comprising dense gliotic tissue with numerous Rosenthal fibres, might

be confused with pilocytic astrocytoma. However, gliosis in the pineal glial cyst differs from pilocytic astrocytoma by lack of cellular heterogeneity and paucicellular, uniformly dense fibrillar feature [18,23]. Difficulties in the interpretation of reactive gliosis, containing Rosenthal fibres, have been noted also in other conditions such as the cyst wall of haemangioblastoma [21].

Histologically, pineal cysts are most often mistaken for a pineocytoma [5,6,15]. The features distinguishing pineal cysts from pineocytoma include presence of an external fibrous capsule, normal pineocytes arranged in lobules with interstitial reactive fibrillary gliosis, absence of pineocytomatous rosettes, and lack of the proliferation index with MIB-1 staining [2,15,18].

In this report, case 1 presented both radiological and histopathological features typical for pineal glial cyst; thus the diagnosis did not present any difficulties. In case 2, the diagnostic difficulties in MRI are rather characteristic for multiseptate cysts, which could also cause some problems in histopathological discrimination. Histologically, the cyst in case 2 was most similar to pineal cystic lesions observed in autopsy cases. There were many cavities of various sizes within areas of gliotic tissue or directly within the pineal parenchyma. Typical ependymal lining was not present. Parenchymal pineal cells were arranged in lobules with an admixture of interstitial glia, calcified deposits and interlobular connective tissue. In accordance with previous reports, it may be concluded that independently of pathophysiological aspects of pineal glial cysts, histopathological findings in asymptomatic and symptomatic cysts are essentially the same.

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