Original Article

Endodermal Cysts of the Central Nervous System: Review of the Literature and a Case Report

Abstract

Context: Endodermal cysts are rare benign developmental cysts lined by mucin-secreting and/or ciliated, cuboidal, or columnar epithelium of probably endodermal origin. **Aims:** Endodermal cysts are rarely intracranial, frequently located in the posterior fossa. Supratentorial location is the most infrequent and only few cases are reported in the literature, included our case. **Settings and Design:** The authors report a case of intracranial supratentorial endodermal cyst with a review of the literature. **Subjects and Methods:** A 40-year-old woman was admitted to our department because of progressive gait disorder for 3 months due to right brachial and crural motor deficit associated to right crural sensory disorder (tactile hypesthesia) and right Babinski response at neurological examination due to an endodermal cyst located in the left frontoparietal convexity. **Discussion** Total resection of endodermal cysts is recommended, despite their location and adhesion to the surrounding structures, due to its high risk of recurrence. Fenestration of the cystic content into the subarachnoid cistern may cause obstructive hydrocephalus or chemical meningism. **Results:** Although rare, surgeons should be aware that these lesions must be differentiated clinically, radiologically, and histologically from other supratentorial cystic lesions.

Keywords: *Central nervous system, endodermal cyst, enterogenous cyst, epithelial cyst, neurenteric cyst, neuroenteric cyst, supratentorial extra-axial cystic lesion*

Fotios Kalfas[1], Claudia Scudieri[2,3]

[1]Department of Neurosurgery Padua University Hospital, Padua, [2]Department of Neurosurgery and Gamma Knife Radiosurgery, IRCCS San Raffaele Scientific Institute, Vita-Salute University, Milan, [3]Department of Neurological Surgery, Galliera Hospitals, Genova, Italy

Address for correspondence:
Dr. Fotios Kalfas, Department of Neurosurgery Padua University Hospital, Padua, Italy.
E-mail: fkalfas@tiscali.it
Dr. Claudia Scudieri, Department of Neurosurgery and Gamma Knife Radiosurgery, IRCCS San Raffaele Scientific Institute, Vita-Salute University, Milan, Italy.
E-mail: claudiascudieri@gmail.com

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Introduction

Endodermal cysts are rare developmental cysts lined by mucin-secreting and/or ciliated, cuboidal, or columnar epithelium similar to the respiratory and the intestinal ones. Although the first case reported in literature by Puusepp[1] dates back to 1934, there has been some controversy in literature regarding their nomenclature also due to the unclear pathogenesis. Historically, they were referred to as "teratomatous," "intestinome," neurenteric, gastrocytoma, and enterogenous cysts. Other terms frequently used in literature are enteric, bronchogenic, or respiratory cysts.[1-5]

Endodermal cysts are usually found in the mediastinum,[6] but they can also rarely occur in any region of the central nervous system, constituting about 0.01% of CNS tumors. They are more common in the lower cervical and upper thoracic spine (0.3%–1.3% of all spinal canal tumors) where they are often associated with dysraphism syndromes,[7] regarding the intracranial site (0.15%–0.35% of all intracranial tumors).[8]

Intracranial endodermal cysts are very uncommon, and in the majority of the cases, they are found in the posterior fossa near the midline, anterior to the brainstem, or within the fourth ventricle. Supratentorial location is the most infrequent among these developmental cysts; to our knowledge, only 66 intracranial supratentorial endodermal cysts cases were reported in the literature, incluing our case.[9-60]

The authors present a complete and concise review of the world's literature about clinical, radiological, histological features and treatment's aspect of intracranial supratentorial endodermal cysts, including our case report.

Subjects and Methods

Review of literature

We performed a review of the current literature using the National Library of Medicine and National Institutes of

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Health based on the keywords: "neuroenteric cyst," "endodermal cyst," "enterogenous cyst," "neurenteric cyst," "epithelial cyst," "enterogenic," "foregut," "respiratory," and "broncho-genic cyst." Only reports in English were considered; spinal and infratentorial endodermal cysts were excluded because of their different pathogenesis.

Only 66 intracranial supratentorial endodermal cysts cases were reported in the literature, including our case.[9-60]

Case report

A 40-year-old woman was admitted our department of neurological surgery because of progressive gait disorder for 3 months due to the right brachial and crural motor deficit associated to right crural sensory disorder (tactile hypesthesia) and right Babinski response at neurological examination. Four years before, the patient underwent magnetic resonance imaging (MRI) examination with incidental diagnosis of nonenhancing extra-axial cystic lesion in the left frontoparietal convexity, hypointense on T1-weighted, and hyperintense on T2-weighted sequences with no contrast enhancement after Gadolinium administration [Figure 1]. The lesion was initially considered to be arachnoid cysts. Due to the absence of signs and symptoms at the neurological examination, the patient underwent clinic-neuroradiological follow-up.

At admission,Brain MRI scans with and without contrast scans showed an increase in volume of the cyst lesion (the maximum diameter was 7 cm vs. 5 cm in the previous radiological examination) with a mass effect on the surrounding structures [Figure 2].

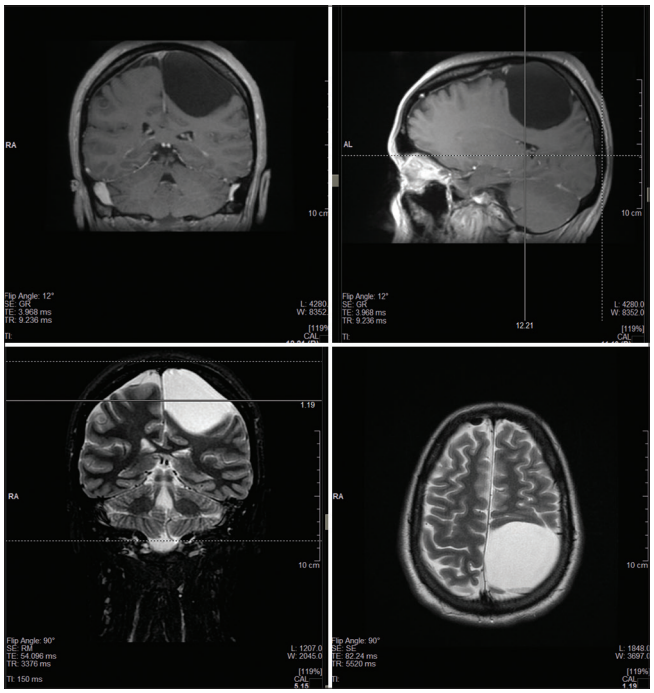

Figure 1: Preoperative magnetic resonance imaging examination shows a nonenhancing extra-axial cystic lesion in left frontoparietal convexity, hypointense on T1-weighted, and hyperintense on T2-weighted sequences

The patient underwent a left parietal craniotomy; the extra-axial nature of the cyst was confirmed. Macroscopically, the lesion consisted of a thin cyst membrane adherent to the dura mater and to the falx cerebri containing a creamy fluid.

The cyst wall was dissected from the underlying brain parenchyma allowing for complete and excision. Postoperative computerized tomography (CT) and MRI scans were uneventful [Figure 3].

All tissues were subsequently fixed in formalin and processed for paraffin sections. Microscopic examination revealed that the cyst wall was lined with a columnar epithelium with a brush border in some areas stain positive with Alcian blue. The cells of the cyst were immunopositive for the epithelial marker cytokeratin 7 and epithelial membrane antigen. Immunostaining for glial fibrillary acidic protein, carcinoembryonic antigen, and S-100 protein was negative. The overall features of the specimen were diagnostic of type A endodermal cyst [Figure 4].

Postoperatively, the patient developed recurrent partial motor/sensory seizures treated with anticonvulsant medication. At 1-month follow-up evaluation, her partial seizures did not recur with anticonvulsant medication, and on neurological examination, the motor/sensory disorders improved.

Results

The patient's features of our literature's review are shown in Table 1.

In our review of literature, the main age at diagnosis was 42 years (range: 0–78 years) with a slight male preponderance (47% females vs. 53% males).

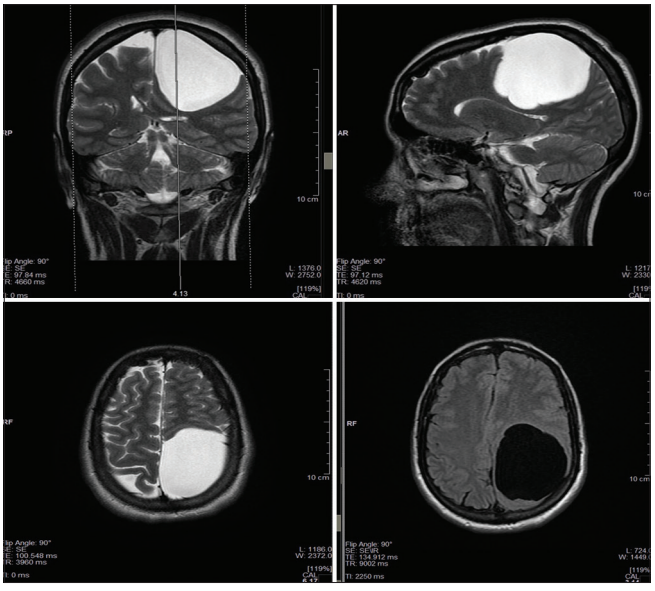

Figure 2: Preoperative magnetic resonance imaging scans show an increase in volume of the cyst lesion

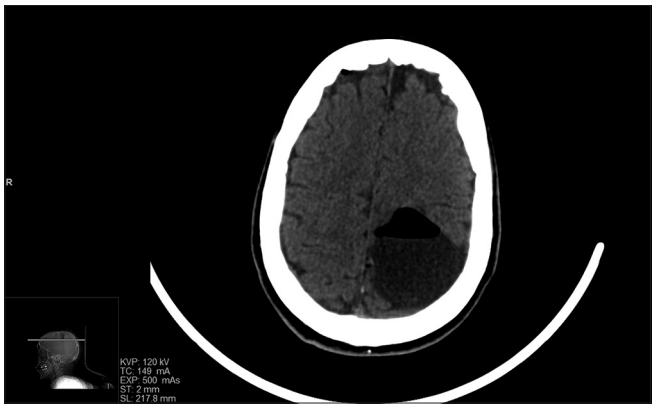

Figure 3: Postoperative computerized tomography scans show a left parietal craniotomy and the complete dissection of the cyst wall from the underlying brain parenchyma

Laterally located endodermal cysts were reported in 47 patients (71%) in contrast to only 16 patients (24%) with midline endodermal cysts. In three cases, we did not find any further information about cysts location. In those laterally located, 28 cases were found in the frontal lobe, 4 cases in the parietal lobe, 5 in the temporal lobe, 10 in the frontoparietal lobe, 1 in the parieto-occipital lobe, and 1 in the parietotemporal one. Twenty-two cases were found on the left side and 23 cases on the right side without any significant side preponderance. Two cases were found of bilaterally location. The main symptoms at the diagnosis were headache observed in 25 patients (38%) and seizures observed in 22 cases (33%). Other symptoms commonly reported are motor/sensory deficit in case of frontoparietal localization, visual loss, hypopituitarism, and cranial nerve palsy commonly related to the suprasellar/parasellar location. Behavior changes and memory loss are frequent in case of involvement of the frontal lobe. One case in the pediatric age was characterized by macrocrania. In a limited number of cases, the clinical symptoms at the moment of the diagnosis were vomiting and other symptoms related to increased intracranial pressure.

All patients underwent surgical treatment and complete excision was achieved in 23 of them. Seven patients underwent cyst recurrence; all of them were related to incomplete excision. Eleven patients experienced postoperative seizures probably related to the chemical irritation due to fluid leakage after incomplete excision or during surgery.

To prevent this complication, we suggest an aspirating cyst's fluid with a needle prior to incise the cyst's wall and protect the subarachnoid space with cotton and warm irrigation.

The most common histological group, following the Wilkins and Odom classification, was Type A with 41 cases (62%); only sixteen cases were Type B (24%). In three cases, malignant transformation was diagnosed, and in only one case, mucinous carcinoma was found. In five cases, we did not find any further information about histological features.

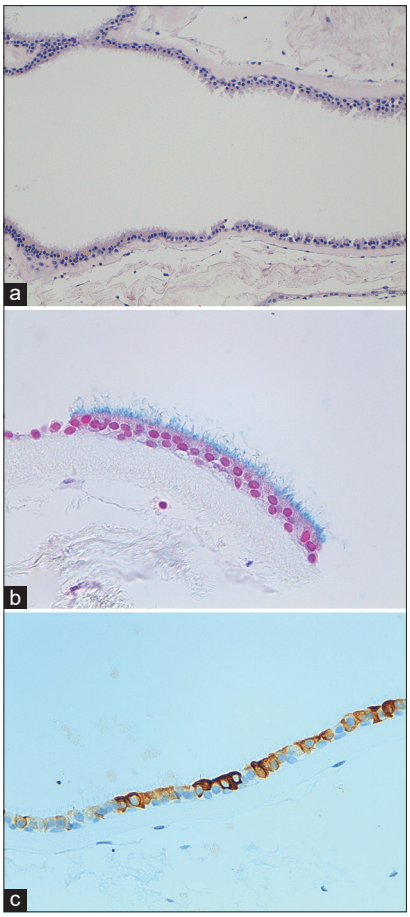

Figure 4: The histological features of the cyst. Hematoxylin and eosin stain revealed that the cyst wall was lined with a columnar epithelium (a) with brush border in some areas stain positive with Alcian blue (b). The cells of the cyst were immunopositive for the epithelial marker cytokeratin 7 (c). The overall features of the specimen were diagnostic of Type A endodermal cyst according to Wilkins and Odom classification (×100)

Discussion

Definition, histopathology, classification, and pathogenesis

Endodermal cysts are fluid-filled cysts lined by columnar or cuboidal ciliated and/or goblet cell epithelium, such as the gastrointestinal one.[61] Their macroscopic appearance varies from yellow or white, thin-walled cysts containing a gelatinous transparent or creamy fluid produced by the epithelium cells. The latter lie on a basement membrane and stain positive with periodic acid–Shiff and Alcian blue. In recent years, immunohistochemistry (IHC) has gained an important role in the diagnosis. Characteristic findings are positivity for cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen, like the embryonic gastrointestinal tract suggesting an endodermal origin of the cysts. They are generally immunonegative for neuronal and ectodermal markers such as neuron-specific enolase, synaptophysin, glial fibrillary acidic protein, and S-100. However, some lesions can include structures derived from mesoderm or neuroectoderm.[62]

Even though this lesion has always been considered histologically benign, malignant transformation is extremely rare but possible, as only eight cases have been reported in the literature. *De novo* carcinomas have been described in six reports which were either focally infiltrative, low-grade adenocarcinoma, or carcinoma *in situ*. Only two cases revealed a malignant transformation during recurrence, probably related to chronic inflammation due to repeated cyst rupture or subtotal resection of the cyst wall that may result in dysplasia and could help to malignant transformation. KRAS mutation may play an oncogenic role.[20,37,54,63-67] As reported by Taek *et al*.[54] in case of malignant transformation in mucin-producing adenocarcinoma, there could be a serum CEA and CA-125 elevations, like other tumors of epithelial origin including lung, ovary, breast, and colorectum that could be helpful also to detect malignant transformation during the follow-up in patients with partially resected endodermal cysts.

Table 1: Endodermal cysts of the central nervous system: Epidemiology, location and clinical features, histological characteristics, and surgical outcome

Features	Total number and %
Epidemiology	
Median age (age range), years	42 (0–78)
Male	35 (53)
Female	31 (47)
Location	
Lateral	47 (71)
Left	22
Right	23
Bilaterally	2
Midline	16 (24)
Not specified	3 (5)
Surgical outcome	
Incomplete excision	18 (27)
Complete excision	23 (35)
Not indicated	25 (38)
Histological classification	
A	41 (62)
B	16 (24)
Not indicated	5 (8)
A plus malignant transformation	3 (5)
Mucinous carcinoma	1 (1)
Clinical symptoms	
Headache	25 (38)
Seizures	22 (33)
Visual loss	8 (12)
Gait disturbance/dizziness	8 (12)
Motor deficit	6
Numbness/paraesthesia	5
Memory loss	5
Behavior changes	4
Incidental	3
Hypopituitarism	3
Cranial nerve palsy	3
Intracranial pressure/vomiting	3
Macrocrania	1

Actually, there is not a classification for intracranial endodermal cysts, so the intraspinal classification one is commonly used.

The classification proposed by Wilkins and Odom[68] in 1976, based on the histological features, identifies three types of endodermal cysts as reported in Table 2.

Despite the many theories proposed to explain the true etiology and the embryological origin of the endodermal cysts, their pathogenesis and the presence of an endodermal lesion within neuroectodermal tissue are still unclear.

One of the theories proposed is based on the failing dissolution of the neuroenteric canal, a transient connection between the primitive neural tube (ectoderm) and the enteric tube (endoderm) which split apart during the notochord formation during the third week of embryogenesis. In this way, some endodermal cells can be incorporated in the neuroectodermal tissue.[69] Since the most cranial extension of the notochord is located at the level of clivus, this theory can easily explain the genesis of the endodermal cysts which lie in the posterior fossa or in the spinal canal but not the intracranial supratentorial ones.

Graziani *et al*.[17] proposed another theory to explain the pathogenesis of the supratentorial endodermal cysts, suggesting an origin from remnants of Seesel's pouch, a transient endodermal outpouch. This theory suggests a common origin of colloid cysts and Rathke's cyst explaining their common immunohistochemistry and can justify the supratentorial endodermal cysts located in the midline (parasellar, retrosellar, and suprasellar); however, it does not explain the genesis of the laterally located supratentorial ones.

Mittal *et al*.[46] during the following years suggested an origin from remnants of endodermal cells that undergo an

Table 2: Histological classification of endodermal cysts of the central nervous system by Wilkins and Odom

Type	Description
Type A	Single layer or pseudostratified cuboidal or columnar, ciliated or not epithelial cells on a basement membrane overlying fibroconnective tissue mimicking the respiratory or gastrointestinal epithelium
Type B	Cysts are richer in connective tissue and contain in addition glands producing mucinous or serous fluid. These cysts may be composed of other tissues including smooth muscle, striated muscle, fat, cartilage, bone, elastic fibers, lymphoid tissue, nerve fibers, and ganglion cells
Type C	In addition to the findings in Type B, may be associated with glial elements such as ependymal cells of the wall

anomalous migration from the neurenteric canal into the ectoderm, justifying the birth of laterally located cysts.

Considering all the above-mentioned hypothesis, we are in full agreement with other authors[17,28,46,69] who consider the suprasellar and parasellar cysts embryologically different from the supratentorial non-midline cysts, probably does not exist a single common cause to explain the pathogenesis of all supratentorial endodermal cysts and all hypothesis could be considered valid.

Radiological features and differential diagnosis

CT scans show a low-density area with no contrast enhancement. MRI remains the imaging modality of choice. Endodermal cysts are well-demarcated lesions that displace but do not infiltrate the adjacent neurovascular structures. On MRI, they are hyperintense on both T1 and T2W sequences but may appear hypointense. This variability in signal intensities is due to the difference in concentration of mucoid material, cholesterol, and protein content within the lesion. Most of the cysts do not enhance following contrast administration.[28] In our case, MRI examination showed a nonenhancing extra-axial cystic lesion in the left frontoparietal convexity, hypointense on T1-weighted, and hyperintense on T2-weighted sequences with no contrast enhancement after Gadolinium administration; the cystic lesion appeared as low-density well-circumscribed area [Figures 1 and 2].

MR spectroscopy can add more information; it can help in presurgical diagnosis and in the differential diagnosis from other lesions by having large N- acetylaspartate (NAA) like peak at 2 ppm chemical shift.[70,71] Endodermal cysts are lined by pseudostratified columnar epithelium and mucin-secreting goblet cells. A large peak at 2 ppm in MR spectroscopy may be due to mucinous content of these cysts. The differential diagnosis for intracranial endodermal cyst includes epidermoid cyst, dermoid cyst, arachnoid cyst, other endodermal cysts (Rathke and colloid cyst), and very rarely ecchordosis physaliphora if retroclival in location.

Arachnoid cysts follow cerebrospinal fluid (CSF) intensity in all sequences. Dermoids usually demonstrate the heterogeneous signal intensity and most have intralesional fat component that gets suppressed on fat-saturated images. Ecchordosis physaliphora is an ectopic notochordal remnant, typically located in the intradural prepontine area that appears hyperintense on both T1 and T2. Stalk connecting to the clivus and bone erosion is the key imaging feature of this lesion.[72] Rathke and colloid cysts can be excluded by their typical location. Colloid cysts, Rathke's cleft cyst, and endodermal cysts are endodermal inclusion cysts that have been named according to their locations.[17] White epidermoid may be difficult to distinguish as it is T1 hyperintense; however, epidermoids show striking restriction of diffusion on DWI that is usually not seen in the endodermal cyst.[73,74]

Clinical symptoms and management

The principal clinical symptoms are related mainly to the local mass effect, so they vary depending on the cyst's location.

Supratentorial endodermal cysts are usually larger in size at the moment of the diagnosis and present later in life than those in the posterior fossa or in the spinal canal. This is likely due to the slow-growing nature of these cysts and the ability to accommodate growth of the cysts in the supratentorial compartment, regarding the smaller volumes of the posterior fossa and spinal canal and the lower tolerance of local mass effect.

In supratentorial endodermal cysts, clinical features are related to the raising intracranial pressure. Patients commonly present with headache, nausea, and vomiting; they may also present focal or generalized seizures or motor/sensory deficit. In case of intraventricular cysts, isn't rare to objectify signs and symptoms related to hydrocephalus.[75] Our patient presented at admission to our department right brachial and crural motor deficit associated to right crural sensory disorder (tactile hypesthesia) and right Babinski response at neurological examination due to the local mass effect to the pre- and postcentral gyri.

Clinical symptoms tend to fluctuate as a result of cyst enlargement due to the active secretion of mucus by the goblets cells followed by spontaneous cyst rupture into the subarachnoidal space.[76] Most cases of endodermal cysts have a long history and slow progression. Several mechanisms are proposed to explain the growth of cysts, including secretion from the epithelial cells of the cyst, differences in osmotic pressure, and the existence of a one-way valve.[77,78] In some cases, sudden onset of the symptoms can be due to intracystic hemorrhage. In literature only five cases are reported of spontaneous intracystic hemorrhage.[44,56,79-81] Of all the reported cases, one showed hemorrhage in the subarachnoid space and four showed intracystic bleeding. Histological examination of the cyst wall found rich blood vessels, which were thought to be the cause of intracystic hemorrhage. Subarachnoid hemorrhage could be associated with the rupture of cyst surface vessels. Both inflammation and leakage of cystic contents could cause the rupture of cyst wall vessels. In these cases, the hemorrhage confused imaging presentation, leading to misdiagnosis.

Fluctuating clinical course or postoperative meningism can also be uncommonly due to chronic, recurrent, aseptic meningitis with polymorphonuclear pleocytosis and negative CSF cultures also known as Mollaret meningitis probably related to subarachnoid leakage of cystic fluid[82] confirmed by the elevated CSF protein content. In these cases, repeated lumbar punctures can relieve symptoms. To prevent this complication, the cystic fluid could be aspirated prior to incision of the cyst's wall.

The consensus for the treatment of symptomatic endodermal cysts is complete resection. Partial resection should be avoided because of the high risk of recurrence. Complete resection, however, might be more difficult primarily due to the possible adhesions to important vascular/neural structures. In case of recurrence, reoperation is indicated for symptomatic recurrence. In our case, the cyst wall was dissected from the underlying brain parenchyma obtaining maximal safe resection.

Partial resection resulted in the rapid overlapping of the remaining cystic wall. Recognizing and electrocoagulating the remaining cystic wall is important in preventing recurrence after subtotal resection in preventing recurrence after subtotal resection. Besides, fenestration of the cystic content into the subarachnoid cistern may cause obstructive hydrocephalus due to its protein-rich content as in our case which macroscopically appeared as milky, creamy fluid. Both the mechanisms can result in early recurrence.[83] Hence, clinical or radiological follow-up is recommended for early detection of recurrence.

Chen *et al*.[53] analyzed some factors correlated with recurrence. In their analysis, limited by the small number of cases, genders, locations of cysts, and ciliated cells noted in pathologic examinations made no contribution to predicting recurrence. In the recurrence group, mucin-secreting cells were found in 66.6% of cases.

Conclusion

Endodermal cysts are rare developmental cysts histologically considered benign, even though malignant transformation is possible, which should be considered in the differential diagnosis with the other cystic lesions of the central nervous system. The definitive diagnosis should be obtained with the help of histology and IHC.

The principal clinical features are highly variable and related mainly to the local mass effect. The aim of treatment of symptomatic endodermal cysts is complete resection due to the high risk of recurrence in case of partial resection. In case of incomplete excision, clinical–radiological follow-up is mandatory for the high risk of cyst recurrence and neoplastic degeneration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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