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Diagnosis difficulty of histiocytosis in the thyroid region of a child: a rare case report with literature review of differential diagnoses

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Abstract

Background: Isolated histiocytosis of thyroid region is very rare; clinical history, exam, and radiological aspects are non-specific, and etiological reasoning is quite difficult considering the tremendous number of differential diagnoses.

Case presentation: This is the case of a 6-year-old girl who came to the emergency room with an acute presentation bulging of the anterior and left lateral regions of the neck. The palpation of the mass showed tenderness; there was no sign of inflammation, nor was there any fistula to the anterior border of the sternocleidomastoid muscle.

The patient was stable. She did not have any signs of compression. The initial blood showed anemia and inflammatory syndrome. She underwent cervical ultrasound exam that showed a mass at the expense of the left thyroid lobe; the mass extends through the sub-hyoid muscles to the lateral cervical region.

A CT scan with and without contrast injection was performed. It showed a heterogenous mass, which seemed centered in the anterior compartment, and from which it extended to the left lateral compartment, as well as the posterior compartment, invading the prevertebral muscles and englobing the carotid and the internal jugular vein.

The patient underwent surgical biopsy. A basal cervical incision was made, dissection with the myo-cutaneous plane. Per-operative observation established that the mass breeched the infrahyoid muscles, as well as the sternocleidomastoid muscle. A biopsy was performed without opening the middle line.

The pathological exam showed an eosinophilic granulomatosis, associated with Stembergoid cells. The immune-histochemical exam concluded that the lesion is histiocytosis. The patient underwent a cervicothoracic and pelvic CT scan to rule out systemic forms. The diagnosis of isolated histiocytosis of thyroid region was confirmed.

The patient underwent hemithyroidectomy, associated with careful dissection of extension of the mass to lateral compartment of the neck. Postoperative exam showed no abnormalities. No dysphonia and no hypocalcemia were observed.

The 8-month follow-up showed satisfactory results, no cervical swelling, and no signs of inflammation or compression. Postoperative naso-fibroscopy was normal.

Conclusions: The most important takeaway message of this work is that methodical approach of neck masses allows to rule out the most aggressive lesions frequently encountered, which allows clinicians to establish thorough diagnosis and management without further delay.

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Keywords: Histiocytosis, Thyroid, Child, Differential, Management

Background

Management of masses thattake place in both anterior and lateral cervical compartments is difficult, since understanding the anatomical content of the different compartments of the head and neck is essential to deduce diagnoses relative to localizations [1].

Case presentation

This is the extremely rare case of histiocytosis of thyroid gland of a 6-year-old girl, which was discovered in an acute episode first, which had an evolution of a lingering neck infection. However, the involvement of more than one cervical compartment at once, as well as the lesion's aggressive aspect, increased diagnostic difficulty.

The palpation of the mass showed tenderness; there was no sign of inflammation, nor was there any fistula to the anterior border of the sternocleidomastoid muscle. Furthermore, the patient did not experience any pus discharge in her throat.

- The patient was stable: no respiratory distress, no signs of sepsis, and no neurological abnormalities.
- The patient did not have any signs of compression: no dysphagia and no dysphonia were depicted.

The initial blood test showed the following: hemoglobin of 8.1; with low VGM: 26; *CRP*: 160; hyperleukocytosis: 16,000, platelet count was normal; and urea and creatinine plasma levels were normal. There was no biological tumor lysis syndrome. TP was normal, and urea and creatinine count was normal. TSH and T4 were normal; calcium and albumin plasma levels were normal as well.

The patient underwent cervical ultrasound exam that showed a mass at the expense of the left thyroid lobe; the mass extends through the sub-hyoid muscles to the lateral cervical region (Fig. 1).

A CT scan with and without contrast injection was performed; it showed a heterogenous mass, which seemed centered in the anterior compartment, and from which it extended to the left lateral compartment, as well as the posterior compartment, invading the prevertebral muscles and englobing the carotid and the internal jugular vein (Fig. 2).

The patient underwent surgical biopsy; a basal cervical incision was made, dissection with the myo-cutaneous plane. Per-operative observation established that the mass breeched the infrahyoid muscles, as well as the sternocleidomastoid muscle. A biopsy was performed without opening the middle line (Fig. 3).

The pathological exam showed an eosinophilic granulomatosis, associated with Stembergoid cells. The immune-histochemical exam concluded that the lesion is histiocytosis.

The patient underwent a cervicothoracic and pelvic CT scan to rule out systemic forms.

The diagnosis of isolated histiocytosis of thyroid region was confirmed.

The patient underwent hemithyroidectomy, associated with careful dissection of extension of the mass to lateral compartment of the neck. Postoperative exam showed no abnormalities. No dysphonia and no hypocalcemia were observed.

The follow-up showed satisfactory results. The 8-month follow-up showed satisfactory results, no cervical swelling, and no signs of inflammation or compression. Postoperative naso-fibroscopy was normal.

The most important takeaway message of this work is that methodical approach of neck masses allows to rule out the most aggressive lesions frequently encountered, which allows clinicians to establish thorough diagnosis and management without further delay.

Discussion

Cervical masses in pediatric population can be the following: congenital, inflammatory, infectious, or neoplastic either benign or malignant [1]. The infectious etiology is generally either acute or chronic [1].

Lateral masses are most frequently infectious. Medical history yields very important data relative to

Fig. 1 Clinical image of an anterior and lateral mass of the neck

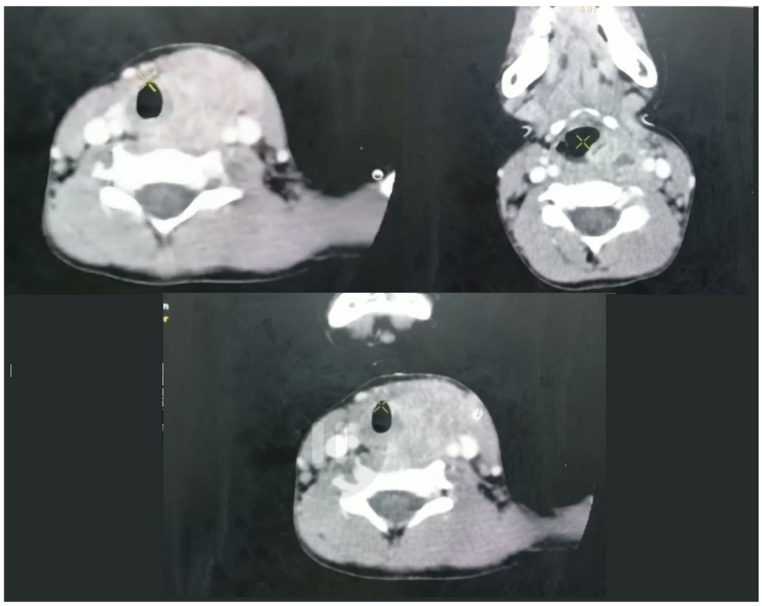

Fig. 2 Axial CT scans showing lesion in the left side of anterior compartment of the neck, extended to the vascular space and the posterior prevertebral spaces

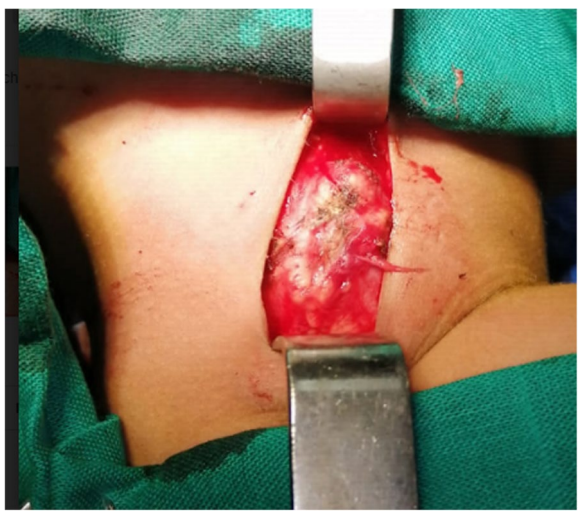

Fig. 3 Preoperative image showing granulomatous mass breaching through the infrahyoid muscles

diagnosis: the age of the patient, the duration, and history of head and neck infections.

The notion of tick-borne diseases is deduced according to residence location and travel to infested zones. Exposition to cats, their excrements, could unveil toxoplasmosis. Consumption of unpasteurized milk and a history of immune-compromised patients, tuberculosis [1].

Moreover, family history could be indicative of multiple endocrine neoplasia type 2 syndrome, neurofibromatosis, autoimmune diseases, vascular abnormalities, and head and neck cancers [1].

Cervical tumors are rarely malignant in children [2–4]. Rhabdomyosarcoma is the most frequently encountered [2–5] (Table 1).

Table 1 summarizes the most frequent malignant processes of the head and neck in children [2, 5].

Thyroglossal cysts are the most frequently encountered branchial arch malformations; the most frequent malformation of the head and neck in children is vascular malformations [1, 3, 4].

Cervical ultrasound, CT scan, and MRI play an important role in diagnosis orientations (Table 2) [3–9].

Fine needle aspiration (FNA) could help guide diagnostic reasoning; it is however overridden when radiological signs of aggressiveness are found [10]. Open biopsy and histological study are key to confirm diagnosis in lesions other than vascular malformations [10].

Histiocytosis of the head and neck represents 5–9 per 1 million patients [10]. It is mostly predominant in males, with a peak occurrence between 1 and 4 years of age [10].

Classifications of histiocytosis have changed in the last 50 years; historically, it was called histiocytosis X. It includes eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease [9].

A new nomenclature classifies Langerhans cell histiocytosis in three categories: single-system single site

Table 1 Most frequent malignant tumors of the head and neck in children [2, 5]

	Diagnosis	Diagnostic and surveillance tools	Treatment
Rhabdomyosarcoma [2, 5]	Is the most frequent common soft tissue sarcoma in children and adolescents • More than 1/3 are located in head and neck region • Peaks: 2–6 years and 10–18 years • Blue cell tumors • Embryonal form at birth: spindle cell or botryoid variants and carries a better prognosis The alveolar form peaks in childhood and adolescence: chromosomal translocation PAX3 FKHR gene has poorer prognosis, especially with metastasis	• Needle or open biopsy. Radiological imaging for staging. (location, size, extent, absence, or the presence of metastasis) CT or MRI or fluorodeoxyglucose PET scan: after 6 weeks of completion of therapy	Multidisciplinary approach Intergroup rhabdomyosarcoma studies (IRS 1-IV): prognostic groups • Multimodal treatment (chemotherapy and either surgery or radiotherapy) • Residual cases could have post-chemoradiotherapy surgery
Neuroblastoma [2, 5]	Most common extracranial malignant tumor in children Less than 5% in the head and neck Arise from the sympathetic cervical ganglia: presents as retropharyngeal or lateral mass Orbital metastatic lesions could be observed Overall survival, with a median follow-up of 4 years: 91% (same in cervical and cervicothoracic neuroblastoma)	Diagnostic: plain radiography, ultrasound, CT, and MRI Metastatic evaluation: bone marrow study, bone scan, scintigraphy with 131 I-meta-Iodo-benzyl-Mandelic (MIBG)	Treatment involves surgery in most cases, with adjuvant chemotherapy and occasional chemotherapy, depending on the stage of the disease Surgery is advised in localized primary or secondary head and neck neuroblastoma, because it provides more favorable prognosis In extensive metastatic lesions, multimodal treatment is decided in multidisciplinary reunions -MIBG is used in high-risk neuroblastoma as an induction therapy
Thyroid cancer [2, 5]	• 2% of cases of thyroid cancers are children and adolescents. Sporadic-differentiated thyroid cancer is the most common. (papillary and papillary follicular) • Female predominance • Postpubertal children • Pure follicular carcinoma, anaplastic and undifferentiated, is extremely rare Medullary thyroid carcinoma should be thought of in children with multiple endocrine neoplasia (MEN) type 2 A and B	Risk factors • Radiation exposure: radiation, leukemia, and lymphoma treatment, especially before 10 years old and in those receiving doses superior to 30 Gy • Iodine deficiency: increases incidence, reduces latency, and influences aggressiveness of radio-induced thyroid neoplasm • Diagnosis: solitary thyroid nodule (20% malignancy) • Initial investigation: TSH, calcitonin, neck ultrasound, and fine needle aspiration (FNA) in children is related to limited data	Therapeutic decision • FNA • Malignancy • Surgery indicated • Indeterminate or inadequate • Repeat in 3–6 months or surgery after discussion of benefit-risk ratio in multidisciplinary reunions Surgery is indicated in children with higher risk of malignancy • < 10 years old •Radiation exposure • Family history of thyroid cancer
Salivary gland malignancy [2, 5]	• -Malignancy is frequent in vascular lesions • -Other types of salivary gland malignancies are rare • More common in older children • Five-year survival 90% (similar to adults)	• Most frequent localization is in the parotid gland, in which the most common histological finding in mucoepidermoid carcinoma • The most common radiotherapy-induced cancer in children is mucoepidermoid • Most submandibular and minor gland lesions are benign Other malignant lesions described include acinic cell carcinoma	Extracapsular dissection with nerve monitoring allows resection of malignant lesions, preserving full nerve function

Table 1 (continued)

	Diagnosis	Diagnostic and surveillance tools	Treatment
Nasopharyngeal carcinoma [2, 5]	• -Common in southern China, Southeast Asia, the Mediterranean Basin, and Alaska • Median age in children: 13 years • -Higher in males	-Factors implicated the following: *Genotype (specific human leukocyte antigen subtypes) *Environment: salted fish high in nitrosamine *Infection (EBV) WHO classification • Type 1: keratinizing squamous cell carcinoma • Type 2: non-keratinizing carcinoma • Type 3: undifferentiated carcinoma	Treatment has been established for adults: height dose radiotherapy to the nasopharynx and involved neck lymph nodes In children, NPC is different with its association with EBV, predominance of type 3, high incidence of advanced stage disease Which has led to increase trials of adjuvant, neoadjuvant, and concomitant chemotherapy
Non-Hodgkin's lymphoma [2, 5]	• 25% of cases in children less than 10 years old • Increasing incidence with age and male predominance • Histological varieties are divided into low, intermediate, and high grade • -High grade is the most prevalent in children • 90% mature B-cell lymphomas. (Burkitt 40% et diffuse large cell 10%) • Immunodeficiency increases the risk, predominance of mature B cell, associates with EBV	Open lymph node excision is the gold standard The use of fine needle biopsy is controversial	Treatment based on aggressive multiagent chemotherapy directed by histology and disease stage. (CHOP-based regimens) Long-term survival enhanced could reach 80%
Hodgkin's lymphoma [2, 5]	Especially in adolescents Only 5% in children under 10 years old No gender difference Association between Hodgkin's lymphoma and EBV infection EBV in genome of Reed-Stemberg cell	+ Open lymph node biopsy is the gold standard + Histologically: 2 categories -Classical Hodgkin's lymphoma (90%) CD15, CD30, Reed-Stemberg -Lymphocyte predominant Hodgkin's: lymphoma (10%), CD20, presentation in early stages, with distinctive subtypes (survival 95%)	• Treatment based on stratification of risk groups: Based on histology, stage, and presentation, number of involved sites, disease blk, and the presence or absence of symptoms • Low-risk classical HL ca be treated by limited cycles of chemotherapy • High-risk classical HL intense chemotherapy regimes with diverse agents, combined with radiotherapy • Free disease survival of 90% have been achieved

Table 2 Clinical and radiological aspects of soft tissue infectious, inflammatory, and congenital lesions in children

		Clinical and histological aspect:	Findings in CT scan and MRI
Infections lesions of soft tissues in children [3, 4]	Infectious cellulitis [3, 4]	• Inflammatory process of the skin and subcutaneous space • Diffuse neutrophil infiltration • Gram-positive cocci generally	• Ill-defined curvilinear or linear areas, with low signal intensity on T1-weighted images, and high signal T2 weighted, associated with reticular appearance in the subcutaneous space • Muscle and bone marrow signals are normal • The presence of fluid collection is not pathognomonic
	Abscess [3, 4]	• Focal collection, necrotic material • Hematogenous or local dissemination	• Well-defined focal collection with low T1 signal and high T2-weighted images • Enhancement of the surrounding rim after intravenous administration of gadolinium • The signal's intensity varies depending on cellular content • Soft tissue edema does not indicate the extension of infection to these structures
	Necrotizing fasciitis [3, 4]	• Rapidly progressive infection • Extensive necrosis of subcutaneous tissue dissecting along fascias • *Streptococcus* serogroup A. Anaerobes, *Staphylococcus*	• Intermediate to low signal intensity, on T1-weighted images, with variable enhancement after gadolinium administration • T2 weighted presents a high signal intensity with thickening of all the compartments • Involvement of deep fascia and intramuscular compartments
	Pyomyositis [3, 4]	• Primary bacterial infection of the skeletal muscle • Immunodeficiency • *Staphylococcus* in 90% of cases	• Primary bacterial infection of skeletal muscle, endemic in tropics, generally in HIV patients • T1-weighted images show increase in volume and subtle increased signal than normal muscle. Enhancement of the rim after gadolinium injection is usual • A focal hyperintense area is generally observed on T2 weighted images, with hypointense peripheral rim
	Tuberculosis [5, 6]	• Generally in lateral compartment of neck • Could invade other structures	• There is no specific radiological aspect of soft tissue tuberculosis

Table 2 (continued)

			Clinical and histological aspect:	Findings in CT scan and MRI
Malformative lesions	Vascular malformations [3, 4, 6]	Arteriovenous malformations and fistulas [3, 4, 6]	• May be clearly pulsatile • May hemorrhage or cause ulceration	• Low signals on both T1- and T2-weighted images due to high flow, serpiginous, the caliber varies. Little mass effect on adjacent structures
		Capillary malformations [6]	• Involve epidermal and dermal layers • Port-wine stain	• Broad very shallow tissue abnormalities involving dermis and epidermis • T1 signal is similar to adjacent muscle and could interrupt subcutaneous tissue • High signal in T2and gadolinium administration
		Venous malformations [3, 4]	• Are the most frequent • May be deep with overlying normal skin • Painful, distended with activity	• T1 similar to or lower than muscular signal • T2 weighting shows an intensely bright signal. (very slow flow). Remain bright after fat suppression • Lobular lesion, grapes-like lesion, with significant mass effect
		Lymphatic malformations [3, 4]	• May be local or diffuse • Involve epidermis and dermis, could be seen in mucosa of oral cavity or tongue	• MRI appearance is similar to venous malformations. Have significant mass effect • T1 low signal or similar signal to adjacent muscle interrupts subcutaneous tissues • T2 is intensely bright • Multiple filled fluid caverns or sinusoid structures
		Hemangiomas [3, 4]	• May be superficial or deep	• T1 signal low or similar to adjacent muscle • T2 moderate increase in signal, less bright and more heterogeneous, irregular shapes grapes-like

Table 2 (continued)

		Clinical and histological aspect:	Findings in CT scan and MRI
	First arch malformations [8]	Parotid, external auditory canal	Usually, branchial cleft anomalies are imaged with MRI with contrast. If an overt pit or fistula is evident on examination and amenable to cannulation, then CT neck with fistulogram and 3-dimensional reformatting is preferred
	Second arch malformations [8]	• Unilateral and right-sided presentations are most common • Is the most common, for which the differential diagnosis includes lymphatic malformation and cervical thymic cyst • In the anterior triangle of the neck, anterior to the sternocleidomastoid muscles. Anterolateral to the great vessels of the neck and may be adherent to the internal jugular vein or possibly protrude between the internal and external carotid arteries	
	Third arch malformations [8]	• Left posterior cervical triangle	
	Fourth arch malformations [8]	• 1–4% of all branchial cleft anomalies • Generally left sided • The pattern could appear from the pyriform sinus and courses through the thyrohyoid membrane to dive into the mediastinum along the tracheoesophageal groove • Endoscopic exam: Fistula in piriform sinus	
	Thyroglossal duct malformation [7, 8]	• Embryologic structure and can be found anywhere along the course of the thyroglossal duct, from the foramen cecum at the base of the tongue to the pyramidal lobe of the thyroid gland	Ultrasound aspect shows a well-circumscribed hypo- or anechoic cystic structure with posterior acoustic enhancement. Septa and debris or internal echoes from protein material, may be present in the absence of infection In the presence of infection, thickened and irregular cyst wall with increased peripheral vascularity may be present. A soft-tissue mass associated with a TDC may represent ectopic thyroid rests or, rarely, a carcinoma
	Epidermoid, dermoid, and teratoid cysts [7]	• Well-defined mass	CT: epidermoid cysts have fluid attenuation; dermoid cysts have a more complex appearance, typically fat attenuation MR imaging: epidermoid cysts are T1 hypointense and T2 hyperintense; dermoid cysts are T1 hyperintense and T2 hypointense

Table 2 (continued)

		Clinical and histological aspect:	Findings in CT scan and MRI
Inflammatory lesions: histological aspect is key to establish differential diagnoses [9]	Langerhans cell histiocytosis. (eosinophilic granuloma)	Infectious: nontuberculous mycobacteria (lepromatous forms), *Leishmania* spp., and others Noninfectious: single system and multicentric system histiocytoses (Table 3)	• CT: scan enhancing soft-tissue masses with surrounding osseous erosion • T1: Hypointense, to isointense • T2: Hyperintense diffuse enhancement
	Non-necrotizing granulomas	• Infectious • Auto-immune • Toxic • Drug: Bacillus et Guérin (BCG) inoculation • Other	No specific radiological aspect
	Necrotizing granulomas	Infectious: *Mycobacterium tuberculosis*, nontuberculous mycobacteria, brucellose, *Aspergillus* spp. Auto-immune: rheumatoid nodule	
	Suppurative granulomas	Infectious: nontuberculosis mycobacterium	
	Foreign body	Suture, starch	

Table 3 Revised classification system of histiocytoses and malignancies macrophage-dendritic cell lineages

Group of histiocytic disorders	Histiocytosis
1: L group	• Langerhans cell histiocytosis (LCH) • Indeterminate cell histiocytosis (ICH) • Erdheim-Chester disease (ECD) (mixed LCH and ECD)
2: C group	Cutaneous LCH ■ Xanthogranuloma (XG) family • Juvenile xanthogranuloma (JXG) • Adult xanthogranuloma (AXG) • Solitary reticulohistiocytoma (SHR) • BCH • GEH • PNH ■ Non-XG family • Cutaneous Rosai-Dorfman disease • Necrobiotic xanthogranuloma (NXG) Cutaneous non-LCH with major systemic component • XG family; xanthoma disseminatum (XD) • Non-XG family multicentric reticulohistiocytosis (MRH)
3: M group	Primary MH malignant histiocytoses Secondary malignant histiocytoses: (following or associated with another hematologic malignancy)
4: R group	• Familial Rosai-Dorfman disease (RDD) - Classical (nodal) - Extra-nodal - RDD with neoplasia or immune disease - Other, non-C, non-L, non-M, non-H histiocytosis
5: H group	• Primary hemophagocytic lymphohistiocytosis (HLH): Mendelian-inherited conditions that lead to HLH • Secondary HLH: non-Mendelian HLH • HLH of unknown origin

(SS-s), single-system multiple site (Ss-m), and multiple site (MS) [9, 10].

Multiple site Langerhans histiocytosis may present in 2 forms: with or without organ involvement. Low-risk organs are lymph nodes, skin, bones, and pituitary gland; high risk organs are bone marrow, the liver, spleen, and the lungs [9].

Besides, a revised classification system of histiocytoses and neoplasms of macrophage dendritic cell lineages defines 5 groups regarding histological aspect and genetic profile (Table 3) [9, 10].

Single-system lesions occur in 65% of cases: 70–82% of bone lesions and 12% of skin lesions. In multisystem forms, the specific involvement of organs affects treatment priorities and prognosis [9].

Histological profile is based on electron microscopy or immunohistochemical reactivity of histiocytes to CD1a and/or S100. Electron microscopy shows characteristic Birbeck granules [10].

Thyroid histiocytosis is generally involved in systemic forms of histiocytosis. Isolated thyroid involvement is extremely rare [9, 10].

Isolated histiocytosis is managed by surgery: in this case, hemithyroidectomy or thyroidectomy. Association in some cases, with adjuvant therapies of chemoradiation, is discussed in multidisciplinary reunions [10].

Conclusions

This is the rare case of thyroid histiocytosis in children. The take-home message of this work is to discuss the differential diagnoses of aggressive masses that are located in the anterior and lateral cervical spaces, regarding frequency and severity, without delay to diagnosis and management.

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KC contributed in clinical management and investigation and analyzed and interpreted the patient data. MI contributed to clinical management of patient. OB operated on the patient and supervised the writing the article. All authors have read and agreed to its content. The authors read and approved the final manuscript.

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Competing interests
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