Inflammatory myofibroblastic lung tumor transforming into intracranial desmoplastic noninfantile ganglioglioma
A case report and literature review
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Abstract
Rationale: Inflammatory myofibroblastic tumor (IMT) of the lung often arises from excessive inflammatory response. It is one of the rare benign tumors of the lung, while desmoplastic noninfantile gangliogliomas (DNIG), on the contrary, are rare intracranial benign tumors often seen in children within the first one and a half years of life.

Patient concerns: We present a 12-year-old girl with 2 months history of none productive cough and right-sided chest pain.

Diagnoses: Computer tomography scan of the chest revealed a soft tissue mass at the right upper lobe which was consistent with IMT. Histopathologic examination confirmed the diagnosis of IMT.

Interventions: Thoracic surgery was successfully carried out and she further received radiotherapy. The patient recovered initially.

Outcomes: Two years later, she complained of seizures during follow-up. Magnetic resonance imaging of the head revealed DNIG. We achieved total resection of the major lesions and she was further treated with radiotherapy. She is currently well and in school.

Histopathologic examination confirmed the diagnosis of DNIG.

Lesions: We speculate that IMT might have transformed into intracranial DNIG through metastatic process or as a result of genetic mutations or chromosomal abrasions.

Abbreviations: CT = computer tomography, DIG = desmoplastic infant ganglioglioma, DNIG = desmoplastic noninfant ganglioglioma, GFAP = glial fibrillary acid protein, IMT = inflammatory myofibroblastic tumor, MRI = magnetic resonance imaging.

Keywords: desmoplastic, ganglioglioma, inflammatory, myofibroblastic, transformation

1. Introduction
Inflammatory myofibroblastic tumor (IMT) of the lung often arises from excessive inflammatory response. It is one of the rare benign tumors of the lung.1–3 The most common origin of this tumor is the lungs, although it can appear in various parts of the body.4 It is mostly found in adults, although sporadically cases have been seen in children.3 Males and females have equal chances of developing this disorder with no geographic or ethnic predisposition.1,5–6 Clinical and radiologic diagnosis before surgery is problematic because of the disparities in clinical and radiologic index. Total tumor removal is crucial to avert malignancy as well as achieve total cure.7–8

Desmoplastic infant/noninfant gangliogliomas, on the contrary, are rare benign intracranial tumors often seen in children within the first one and a half years of life.9–12 These tumors often have distinct radiologic feature such as enhancing small solid segments and nonenhancing huge cystic segments.9–12 Total surgical resection is often advantageous, although total surgical resection is achievable in about 56% to 70% of cases.9,10,13 In case of partial resection, it is advisable to add adjuvant therapy. Survival rate in patients who have total resection is usually between 8.3 and 20 years.14

The most distinctive histopathologic finding in desmoplastic infant tumor (DIG) is the fibroblastic differentiation as well as desmoplastic low-grade glial-neuronal tumor with both synaptophysin and glial fibrillary acid protein (GFAP) positivity.13 This distinguishing feature permits the development of a complex extracellular matrix and intracellular cytoskeleton in the neoplastic cells.16,17 We present a case of IMT transforming into intracranial desmoplastic noninfantile ganglioglioma (DNIG).
2. Case report
We present a 12-year-old girl with 2 months history of none productive cough. She was apparently well until 2 months ago when the above started. The cough was nonproductive and worsens as the weather got colder with no associated fever. She however had severe chest pain at the right side. Her previous medical history was unremarkable and her immunization was complete according to her age. Her parents denied any family history of chronic pulmonary disease. Chest examination revealed quite reduced chest movement at the right side with dullness to percussion and reduced air entry as well as a friction rub. All the other systems were essentially normal. Routine laboratory and ancillary investigations were normal. The results of tumor markers of inflammation revealed an neuron specific enolase of 16.07 ng/mL with negative alpha-fetoprotein, carcinoembryonic antigen, and nonsmall cell lung cancer antigen.

Computer tomography (CT) scan of the chest revealed a soft tissue mass at the right upper lobe, measuring about 5.5 x 5.1 cm with inner annular calcification (Fig. 1, A–D). The tumor extended into the mediastinum with significant compression on the right upper bronchus. There was significant hilar and mediastinal lymph node enlargement without mediastinal shift or bilateral pleural effusion. The heart was normal and no pericardial effusion. Based on the history and radiologic finding above, a working diagnosis of lung cancer was made to rule out pulmonary tuberculosis and other inflammatory disorders. The tumor was resected via transthoracic approach. Intraoperatively, a sizable portion of tumor was located at the right upper lobe with mediastinal extension as well as right middle lobe and right upper bronchus compression. After operation, the patient further received radiotherapy.

Microscopic examination of specimen obtained during surgery revealed that the lesion had proliferative inflammatory cells and spindle cells. There were abundant plasma cells, lymphocytes as well as proliferation of myofibroblast or fibroblast at the background. There was also infiltration of inflammatory cells and hyperplastic myofibroblasts or fibroblast with some sections with glass-like masses of deformation, scattered calcification, as well as inflammatory pseudotumor formation. Fluorescent in situ hybridization detection examination revealed no ALK gene translocation. Immunohistochemistry examination also revealed proliferation of myofibroblasts or fibroblasts with smooth muscle antibodies (SMA) (+), Desmin (+), MSA (+), activin receptor-like kinase 1 (ALK-1) (+), CD34 (--), Bcl-2 (--), CD99 (--), S-100 (--), Ki-67 (+, 5%), and plasma cells with IgG (+). The patient recovered well and discharged home 2 weeks after surgery.

On the 4th follow-up visit (2 years after the surgery), the patient complained of seizures which were tonic clonic in nature and lasted.
for about 10 minutes. The frequency of the seizures becomes unbearable to the parents. She was then referred to the neurosurgery clinic. Neurologic examination was unremarkable. Routine laboratory and ancillary investigation were all normal. Repeated investigation of tumor markers of inflammation was negative.

Magnetic resonance imaging (MRI) of the head revealed scattered multiple nodules with diverse signal intensities (Fig. 2, A–F). The lesions were seen as hypointense on T1-weight imaging and hyperintense on T2-weight imaging. An enhanced scan also showed significant enhancement of the lesions. The largest one was located at the right temporal lobe measuring about 2.7 cm in all diameters. The ventricle shape and size were normal with no midline shift. Base on the history and radiologic findings above, a working diagnosis of metastatic inflammatory myofibroblastic lung tumor was made to rule out parasitic infections and other diseases. CT scan of the chest revealed no tumor recurrence.

Intraoperatively, the lesion at right temporal lobe was resected via the subtemporal approach and the frontal lesions were resected via the right frontal approach. We saw multiple grayish white, solid lesions measuring about 2 × 2 cm in diameter located in the temporal lobe and the right frontal lobe. We did not see any feeding blood vesicle to the tumors. We attained total tumor resection in both approaches. The patient recovered well postoperatively. Pathologic findings were consistent with desmoplastic ganglioglioma World Health Organization (WHO), grade 1 (Fig. 3 A–D). Confirmation immunohistochemistry revealed Synaptophysin (+), neuronal nuclei (NeuN) (+), neurofibromatosis (+), GFAP (+), oligodendrocyte transcription factor (+), SMA (+), alphathalassaemia/mental retardation syndrome X-linked (+), MIB-1 (+, <3%), ALK-1 (−), CD34 (−), isocitrate dehydrogenase-1 (−). The patient was discharged home 2 weeks after the operation. Three months later, the left temporal and cerebellar tentorium lesions were successfully resected via a second surgery. Pathologic diagnosis was consistent with the previous one. She was further treated with radiotherapy because of small satellite lesions that were inaccessible during surgery. Two years follow-up revealed no tumor recurrence. She is currently well and in school.

3. Discussion

The IMT is a rare lung tumor which comprises of irregular pattern of inflammatory and mesenchymal cells such as inflammatory pseudotumor plasma cells, histiocytes, lymphocytes, and fibroblasts.[1,4] The most common site of this tumor is the lungs, although it can appear in various parts of the body. It is mostly found in adults although sporadically cases have been seen in children.[1,3] The age of our case is therefore very puzzling. Males and females have equal chances of developing this disorder with no geographic or ethnic predisposition.[5,6] A few authors still do not accept that the etiology of IMT as an inflammatory reactive disorder or neoplasm, while some suggested that this disorder is a neoplasm with benign or low-grade malignancy. The precise etiology of this disorder is unclear.[17] Clinically, patients usually present with cough, dyspnea, hemoptysis, chest pain, fever and fatigue, and sometime weight loss and anorexia in very sporadic cases.[18,19] Furthermore, a sizable number of cases present with vague symptoms; hence, the diagnosis is made parenthetically on chest X-ray done for alternative purposes.[18,19] Radiologic evaluation of patients is
usually inconstant and nonspecific. The lesions are usually smooth or bumpy and situated at the periphery with high penchant of the lower lobes. In our case, the lesion was solitary and located at the upper lobe. On CT scan, the lesions are often seen as a heterogeneous nodule or mass with inconstant contrast enhancement. CT scan identifies the tissue or cystic behavior of this lesions as well as vascular components and locoregional extension. Calcifications and cavitations are seen in sporadic cases. Pleural effusion and atelectasis occur in about 8% to 10% of patients and occasional the lesions may extend to the hilum, mediastinum, pleura, or diaphragm.

Using clinicopathologic features of inflammatory pseudotumor of the lung. Matsubara et al classified IMT into 3 subtypes such as organizing pneumonia, fibrous histiocytoma, and lymphoplasmacytic. Organizing pneumonia type has intraalveolar lymphohistiocytic inflammation which transfigures into intra-alveolar fibrosis peripherally and interstitial fibrosis centrally due to proliferation of fibroblasts. With this transformational changes within the lungs, we think similar changes are possible in the brain when during metastasis. The gold standard management of pulmonary IMT is total surgical resection. Total tumor removal is crucial to achieve total cure. However, some authors have recorded recurrence years after surgical resection as well as mortality.

Studies have shown that immunohistochemistry indicates often a reaction to vimentin and smooth muscle actin. ALK is detectable in about 50% of cases with cytoplasmic staining, infrequently with the nuclear membrane. Pathologically, the mode of tumor development, the low mitotic index, the polyclonality of lymphoid markers, and the negativity of CD34 distinguish this disorder from other lesions. Some of the differential diagnoses are desmoid fibromatosis, fibrosarcoma, leiomyoma, and malignant fibrous histiocytoma. Almost all the authors who have reported cases on IMT clearly indicated that the disease is a benign, non-metastasizing proliferation of myofibroblasts with a potential for recurrence and persistent local growth. This report therefore makes our case much more interesting.

On the contrary, DIGs are grouped under desmoplastic neuroepithelial tumors which are classified as WHO grade I tumors. The male to female ratio of DIG is 1.7:1. The ages of all the cases reported in literature are between 8 days and 24 months. A noninfantile variant of this intracranial neoplasm has also been reported, although this type is much rarer. The ages of all the variant cases in literature are between 5 and 25 years. Therefore, our case also falls into the DNIG category, although we believe the etiology is from metastasis of her IMT or due to genetic mutations or aberrations. There are only few reports in the literature on the genetic aberrations in DIG. Park et al observed breakpoints on a variety of chromosomes in a single case of DIG but did not state aberrations on chromosomes 8 or 13 as the etiology. Molecular genetic studies also revealed that DIGs do not display any allelic loss on
chromosomes 17p and do not carry TP53 gene mutations. Furthermore, research has proven that normal karyotype or nonclonal abnormalities exist in DIGs. Genomic losses have been seen at 5q13.3, 21q22.11 (TMEM50B, DNAJC28), and 10q21.3 both in DIGs while high-copy gains seem to be lacking or exceptionally rare. Moreover, EGFR and MYCN amplifications have also been proven in DIG. Besides, chromosomal gains affecting the region harboring the BRAF protein have been observed in the desmoplastic area of DIGs. All these findings suggest that the DIGs can occur as a result of gene mutation of chromosomal aberration.

Clinically, DIG usually manifests as macrocephaly as a result of long standing hydrocephalus in about 40% of cases, seizures in about 20% of cases, bulging fontanelles, bony bossing, visual disturbance, as well as paresis. Neonatal manifestation with intracranial hemorrhage has also been seen. On CT scans, DIG appears as a huge, hypodense, or slightly hyperdense lesion with a superficial segment that extends into the superimposing meninges and displays extreme contrast enhancement. The cystic segment is often situated deeper, while the solid segment is peripheral. MRI is the gold standard diagnostic modality for DIG as it assists in recognizing the manifestation of a large supratentorial tumor involving more than 1 lobe, a lesion consisting of a large cyst often hypointense on T1 weighed and hyperintense T2-weighted as well as smaller solid lesions also seen on T1 and T2 weighed as isointense cortical component with intense enhancements, and apposition of the superficial solid component to a meningeal surface, with enhancement along the dura. Furthermore, a greater proportion of the tumor comprises of large cysts, with minimal surrounding vasogenic edema. In most cases, the lesions occupy 1 to 2 lobes or even the whole hemisphere. On MRI, differential diagnosis often includes pleomorphic xanthoastrocytoma, primarily due to its leptomeningeal involvement, ganglioglioma, and primitive neuroectodermal tumor.

The gold standard treatment for DIG is total or radical resection. The site of the lesion and the manifestation of multiple huge cysts surrounding the lesion contributes to the outcomes of total or radical resection. However, about 56% to 70% of cases had total or radical resection in the literature and in case where total resection is not possible, it is advisable to add adjuvant therapy. The principal impediment to total resection is due to the far-reaching nature of lesions or bilateral extension. Although the lesions in our case were deep seated, we were able to achieve total resection via 2 approaches in 1 surgery. Radiotherapy was also very helpful in the management of our case.

4. Conclusion
This case demonstrates a strong association between of IMT and intracranial DIG. We speculate that IMT might have transformed into intracranial DIG through metastatic process or due to genetic mutations or aberrations. Although the lesions in our case were deep seated, we were able to achieve total resection via 2 approaches in 1 surgery. Radiotherapy was also very helpful in the management of our case.

Author contributions
All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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