Genetic Testing and Immunotherapy for Intracranial Inflammatory Myofibroblastic Tumor: A Case Report

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Abstract: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor that can develop in numerous organs, most commonly in the lungs and rarely in the brain. Here, we reported a 55-year-old patient with nasopharyngeal IMT and the recurrence in the skull base, slope and pterygoid sinus who underwent cranial base and slope tumor resection. Postoperative magnetic resonance imaging (MRI) and multiplex immunohistochemistry (mIHC) showed tumor recurrence and metastasis to the intracalvarium. While genetic testing revealed no significant related gene mutations, tertiary mutations in NSD1 and SOX9 genes were identified in the tumor tissues. The patient achieved partial remission after receiving 7 cycles of immunotherapy (toripalimab 240 mg for 1 cycle followed by 6 cycles of sintilimab 200 mg), and MRI examination indicated an almost complete remission of intracranial IMT after 16 cycles of immunotherapy. In summary, the novel class of immune-targeted agents may be effective in clinical management of rare intracranial IMT.

Keywords: inflammatory myofibroblastic tumor, sintilimab, multiplex immunohistochemistry, magnetic resonance imaging, immunotherapy

Introduction

Inflammatory myofibroblastic tumor (IMT), also known as inflammatory pseudotumor and plasmacytoid granuloma, is a tumor commonly occurring in the lungs, abdomen, skin, soft tissues, genital system, and mediastinum.1,2 Its origin, etiology and behavior remain a matter of debate. While metastases have been reported in up to 5% of IMT cases, potential kinase mutations, most commonly involving anaplastic lymphoma kinase (ALK), have been identified in these tumors.3,4 Recurrent metastasis of IMT may be associated with incomplete resection of the lesion, involvement of infiltrating adjacent vital organs, and TP53 expression in tumor cells.

Herein, we reported a rare case with intracranial IMT who achieved complete remission (CR) after receiving immunotherapy. This report provided important guiding significance to clinical treatment of the disease.

Case Presentation

A 55-year-old female was admitted to our hospital with recurrent IMT and invasion of skull base, slope and sphenoid sinus after tumor resection. On January 13th, 2019, the patient had a sudden onset of slurred speech without obvious
incentive and her condition improved spontaneously after 30 seconds. She was treated with mannitol and vasodilator in Weifang Yidu Central Hospital, but the symptoms were not significantly alleviated. The patient was then referred to Shandong Provincial Hospital and underwent cranial base and slope tumor resection through nasal endoscopy on

**Figure 1** Representative magnetic resonance imaging (MRI) scans. MRI images taken during radiotherapy, at the end of radiotherapy, after 2 cycles of immunotherapy, after 7 cycles of immunotherapy, after 12 cycles of immunotherapy, after 16 cycles of immunotherapy, and during follow-up were shown respectively.

![Representative MRI scans](https://doi.org/10.2147/OTT.S343562)

**Figure 2** (A) Hematoxylin and eosin staining of the recurrent lesions. (B) The expression of CD8, PD-1, PD-L1, and CD68 in resected tumor tissues was detected by multiple immunohistochemistry (mIHC). Nuclei (blue) were counter-stained by DAPI. Magnification ×200. (C) Quantification analysis of data in B. (D) The frequencies of two shared pathogenic mutations in the recurrent lesions.
March 12th, 2019. Postoperative pathological examination confirmed the diagnosis of IMT. She was discharged with a good postoperative recovery and did not receive any further treatment after surgery.

On April 9th, 2019, the patient was admitted to Shandong Institute of Medical Imaging. Craniocerebral magnetic resonance imaging (MRI) (April 15th) showed abnormal thickening of the middle cranial fossa region, skull base and right temporal meninges (Figure 1), suggestive of tumor recurrence and metastasis following surgery. Hematoxylin and eosin staining suggested inflammatory myofibroblastoma, with abundant cells and active growth (Figure 2A). Meanwhile, multiplex immunohistochemistry (mIHC) revealed a relatively high infiltration of CD8+/CD68+ lymphocytes as well as a high expression of PD-L1 (SP142) in the tumor tissues (Figure 2B). Moreover, quantitative analysis of tumor cells, macrophages and other subsets of immune cells found that the proportion of CD8+, PD-L1+, CD68+, CD8+PD-1+, CD8+PD-1+, and CD68+PD-L1+ cells in the tumor region was 47.3%, 98.9%, 49.8%, 13.2%, 33.9% and 49.7%, respectively, while the stromal region harbored the different percentage of CD8+ (43.2%), PD-L1+ (98.7%), CD68+ (33.5%), CD8+PD-1+ (8.7%), CD8+PD-1- (34.4%), and CD68+PD-L1+ cells (33.4%) (Figure 2C).

After consultation in the radiotherapy department of our hospital, the patient received radiotherapy with a total dose of 54 Gy in 27 fractions between April 17th and May 23rd, 2019. This trial was approved by the Ethics Committee of Shandong Cancer Hospital, and written informed consent was obtained from the patient. During radiotherapy, next generation sequencing (NGS) of her blood cells and paraffin-embedded tissues was carried out using a 543 cancer-related gene panel (Genecast, Wuxi, China) to identify the possible gene mutations suitable for immunotherapy. As shown in Figure 2D, the frequency of NSD1 c.3286C>A p.H1096N and SOX9 c.1309C>T p.R437C in the tissues was found to be 3.2% and 2.73%, respectively. MRI (May 23rd, 2019) revealed that at the end of radiotherapy, IMT invaded the skull base and brain with right dural metastasis after surgery (Figure 1).

The patient was then treated with immunotherapy for further suppressing IMT. After excluding the immune contraindications, she was first given intravenous drip of Toripalimab (240 mg) for 1 cycle, and no obvious side effects were observed. Thereafter, she was administered with Sintilimab (200 mg) for another cycle, and a subsequent craniocerebral MRI examination (August 2nd, 2019) showed that the tumor was shrinking. Following another 7 cycles of immunotherapy (Sintilimab, 200 mg), most of the lesions were in remission (March 2nd, 2020). On July 27th, 2020, craniocerebral MRI demonstrated that the lesions had a near-CR rate of 98% after 12 cycles of Sintilimab 200 mg (Figure 1). Since then, the patient visited our hospital monthly for receiving Sintilimab 200 mg. After 16 cycles of Sintilimab 200 mg, the curative effects of the patient almost reached CR with no significant changes in the tumor (January 4th, 2021). In this case, the immunotherapy was well tolerated with no significant toxic and side effects. And no other therapy was given after the end of the treatment with Sintilimab. On April 12th, 2021, craniocerebral MRI demonstrated an improvement in postoperative nasopharyngeal IMT with invasion of the skull base, brain and right dural metastasis (Figure 1). The clinical and disease course of the patient is illustrated in Figure 3.
<table>
<thead>
<tr>
<th>Age (Years)/Sex</th>
<th>Presentation</th>
<th>Tumor Primary Site</th>
<th>IHC</th>
<th>Gene Mutation</th>
<th>Recurrence</th>
<th>Tumor Metastasis Site</th>
<th>Treatment</th>
<th>Follow-up and Prognosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>55/F</td>
<td>A sudden slurred speech</td>
<td>Nasopharynx</td>
<td>Highly expressed PD-L1</td>
<td>Tertiary mutations in NSD1 and SOX9 genes</td>
<td>1 month</td>
<td>Skull base, slope and pterygoid sinus</td>
<td>Surgery, radiotherapy and immunotherapy (PD-L1 inhibitor Sintilimab)</td>
<td>Better than before to date</td>
<td>This case</td>
</tr>
<tr>
<td>19/M</td>
<td>Macroscopic hematuria and progressive anemia</td>
<td>Bladder</td>
<td>ALK pos</td>
<td>NA</td>
<td>7 months</td>
<td>Lung and left iliac bone and</td>
<td>Surgery and targeted therapy</td>
<td>Complete remission</td>
<td>Bonvini et al, 2021</td>
</tr>
<tr>
<td>16/M</td>
<td>NR</td>
<td>Right chest wall with pleural involvement</td>
<td>ALK neg, highly expressed PD-L1</td>
<td>TFG-ROS1 fusion, an acquired G2032R mutation in the TKD of ROS1 and MAPK1 amplification</td>
<td>Continuing progression</td>
<td>Brain, right triceps</td>
<td>Antiinflammatory therapy, chemotherapy, targeted therapy and immunotherapy (PD-L1 inhibitor Nivolumab)</td>
<td>Died of respiratory complications</td>
<td>Carcamo et al, 2021</td>
</tr>
<tr>
<td>40/M</td>
<td>Dyspnoea and productive cough</td>
<td>Upper lobe of right lung</td>
<td>ALK pos</td>
<td>TPM4-ALK fusion</td>
<td>Transient improvement and continuing progression</td>
<td>Hilar lymph nodes, right trapezius muscle, left frontal lobe, left adrenal, left gluteal</td>
<td>Chemotherapy, radiotherapy and targeted therapy</td>
<td>Dead</td>
<td>Wong et al, 2020</td>
</tr>
<tr>
<td>59/M</td>
<td>Consistent fatigue</td>
<td>Medium lobe of right lung</td>
<td>ALK neg</td>
<td>NA</td>
<td>Continuing progression</td>
<td>Bone and abdominal cavity</td>
<td>Targeted therapy</td>
<td>Stable condition on follow-up 9 months</td>
<td>Liu et al, 2019</td>
</tr>
<tr>
<td>Age</td>
<td>Symptom(s)</td>
<td>Site</td>
<td>ALK Status</td>
<td>Time After Surgery</td>
<td>Treatment</td>
<td>Outcome</td>
<td>Reference</td>
<td></td>
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<tr>
<td>81/M</td>
<td>Anal pain</td>
<td>The posterior rectal wall</td>
<td>ALK neg</td>
<td>2 months after surgery</td>
<td>Liver</td>
<td>Surgery</td>
<td>Dead</td>
<td>Shimodaira et al, 2020</td>
<td></td>
</tr>
<tr>
<td>76/M</td>
<td>Upper back pain and motor weakness</td>
<td>Upper lobe of right lung</td>
<td>ALK neg</td>
<td>NA</td>
<td>Right renal hilum</td>
<td>Hormonotherapy and radiotherapy</td>
<td>Improvement in symptoms on follow-up 1 month</td>
<td>Na et al, 2018</td>
<td></td>
</tr>
<tr>
<td>55/M</td>
<td>Left pneumonia</td>
<td>Lower lobe of left lung</td>
<td>NA</td>
<td>3 months after first surgery</td>
<td>Lingula, lung and liver</td>
<td>Surgery and radiotherapy</td>
<td>The patient was referred to another oncological center.</td>
<td>Rodrigues et al, 2017</td>
<td></td>
</tr>
<tr>
<td>37/F</td>
<td>Cough and stridor</td>
<td>Upper lobe of left lung</td>
<td>ALK pos</td>
<td>1 year after first surgery</td>
<td>Uterine</td>
<td>Surgery</td>
<td>Dead 1 year after second surgery</td>
<td>Zhang et al, 2018</td>
<td></td>
</tr>
<tr>
<td>18/F</td>
<td>Headaches</td>
<td>Lung</td>
<td>ALK pos</td>
<td>Continuing progression</td>
<td>Brain</td>
<td>Targeted therapy</td>
<td>Alive and well on follow-up 2.5 years since primary diagnosis</td>
<td>Yuan et al, 2017</td>
<td></td>
</tr>
<tr>
<td>43/F</td>
<td>Heart failure symptoms</td>
<td>Small intestinal</td>
<td>ALK neg</td>
<td>1 year</td>
<td>Left ventricle, stomach, liver, vertebra, and pelvic bones</td>
<td>Surgery and chemotherapy</td>
<td>Dead 9 months after surgery</td>
<td>Zorinas et al, 2017</td>
<td></td>
</tr>
<tr>
<td>16/F</td>
<td>A localized left shoulder mass</td>
<td>Left shoulder</td>
<td>ALK pos</td>
<td>45 months</td>
<td>Left clavicle, the arm, and the anterior chest wall soft tissues</td>
<td>Surgery, chemotherapy, radiotherapy and targeted therapy</td>
<td>Remains in complete remission on follow-up 3 years</td>
<td>Gaudichon et al, 2016</td>
<td></td>
</tr>
<tr>
<td>49/F</td>
<td>Cough</td>
<td>Lower lobe of left lung</td>
<td>ALK pos</td>
<td>ALK-gene rearrangement</td>
<td>4 months</td>
<td>Surgery and targeted therapy</td>
<td>NR</td>
<td>Sethi et al, 2015</td>
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</table>

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</tr>
</thead>
<tbody>
<tr>
<td>28/F</td>
<td>Post-prandial abdominal pain</td>
<td>Abdominal extensive solid masses involving multiple viscera</td>
<td>ALK neg</td>
<td>NA</td>
<td>Continuing progression</td>
<td>Vertebral body, liver and peritoneum</td>
<td>Surgery and chemotherapy</td>
<td>Dead</td>
<td>Kim et al, 2015</td>
</tr>
<tr>
<td>27/F</td>
<td>A painless palpable mass in the upper outer quadrant of the right breast</td>
<td>Right breast</td>
<td>ALK neg</td>
<td>NA</td>
<td>2 years</td>
<td>The upper inner quadrant of the right breast and right cervical area</td>
<td>Surgery</td>
<td>NR</td>
<td>Choi et al, 2015</td>
</tr>
<tr>
<td>36/M</td>
<td>Hematochezia, tenesmus, and constipation</td>
<td>Rectum</td>
<td>ALK pos</td>
<td>NA</td>
<td>18 months</td>
<td>The pelvic floor muscles, sacroccocyx, pre-sacral fascia</td>
<td>Surgery and chemotherapy</td>
<td>Follow-up every 6 months and disease-free</td>
<td>Sun et al, 2014</td>
</tr>
<tr>
<td>26/M</td>
<td>Chronic nonproductive cough</td>
<td>Mediastinum</td>
<td>ALK neg</td>
<td>NA</td>
<td>Continuing progression</td>
<td>Lymph nodes and the thoracic vertebra</td>
<td>Hormonotherapy and chemotherapy</td>
<td>No radiological evidence of tumor progression or recurrence for 7 months</td>
<td>Kubo et al, 2012</td>
</tr>
<tr>
<td>52/M</td>
<td>Dyspnea and cough</td>
<td>Upper lobes of bilateral lung</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>Left adrenal gland</td>
<td>Surgery</td>
<td>Alive and well, without recurrence on follow-up 1 year</td>
<td>Carillo et al, 2011</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALK, anaplastic lymphoma kinase; F, female; M, male; NA, not available; neg, negative; NR, not reported; pos, positive.
Discussion
IMT is a relatively rare tumor of mesenchymal origin that is common in children and adolescents. It can develop in various organs, with the lung and liver being commonly affected and the skull being less involved.\textsuperscript{5,6} Surgical resection is the most common treatment for IMT.\textsuperscript{4} In this case, while the patient was first diagnosed with nasopharyngeal IMT, the tumor recurred and metastasized to the brain after tumor resection. Genetic testing failed to identify representative gene mutations in IMT. However, the patient was found to harbor tertiary mutations in NSD1 and SOX9 genes as well as a high expression of PD-L1 in the tumor tissue. SOX9 acts as a key determinant of cancer cell plasticity. NSD1 is a histone methyltransferase containing the catalytic domain of SET, and its abnormal expression could be closely associated with Sotos syndrome. It has been reported that NSD1 affects chondrocyte differentiation by regulating the expression of Sox9.\textsuperscript{7} To date, the significance of mutations in NSD1 and SOX9 genes in IMT has yet to be defined.

Identification of underlying kinase mutations, including those in ALK, has provided a potential targeted therapy option for patients with unresectable and/or advanced IMT. It has been shown that not all IMT patients harbor actionable mutations. In the past 10 years, a total of 18 cases with metastatic IMT have been reported;\textsuperscript{8–25} most of them received surgical resection for primary IMT, while undergoing radiotherapy, chemotherapy and/or targeted therapy for metastatic tumors (Table 1). In one study, Carcamo et al showed that PD-L1 was expressed in 50% of the tumor cells in a 16-year-old male patient who failed to respond to PD-L1 inhibitor Nivolumab.\textsuperscript{9} In this case, we found that treatment with Sintilimab can block the binding of PD-1 with PD-L1 and alleviate tumor cell suppression via immune T cells. Sixteen cycles of immunotherapy led to a significant inhibition in the tumor cells of the patient. Sintilimab is PD-1 monoclonal antibody that has recently been approved for cancer treatment.\textsuperscript{26} In China, Phase I/II/III clinical trials of Sintilimab for the treatment of various solid tumors are being conducted.\textsuperscript{27–29} Wang et al have reported that Sintilimab possesses stronger anti-tumor activity with an acceptable safety profile in vivo as compared to certain monoclonal antibodies,\textsuperscript{30} while it obviously has some inevitable side effects and causes potential damage to patients, including pneumonia, diarrhea, colitis, hepatitis, and nephritis. At present, there is no report on research of the effects of Sintilimab and Toripalimab on IMT. Surgery remains predominant in clinical management of intracranial IMT due to the lack of definitive treatment and its unknown pathogenesis. In addition to radiotherapy, long-term treatment with clarithromycin can be administered when ALK1 and immunoglobulin deficiency are diagnosed, or when chronic inflammation worsens the patient’s condition.\textsuperscript{31} This study provides the first demonstration that Sintilimab exerts a good therapeutic effect on a patient with recurred IMT and intracranial metastasis.

Conclusion
The presence of tertiary mutations in NSD1 and SOX9 genes could potentially serve as an indicator for the diagnosis of IMT. Meanwhile, Sintilimab may be a good choice for immunotherapy against the recurrence and metastasis of IMT.

Ethics and Informed Consent Statements
This study was approved by the Ethics Committee of Shandong Cancer Hospital. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Author Contributions
All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors declare that they have no conflict of interest.
References


