

Regression of an ALK-Negative Cerebral Inflammatory Myofibroblastic Tumour by Steroid Therapy: A Case Report and Literature Review

Yijun Ge^{1,2,#}, Lili Wu^{2,#}, Chengjuan Xie³, Qian Da⁴, Ying Dai^{2,*}

¹The Sleeping Disorder Department, Shanghai General Hospital Bengbu Hospital, Bengbu, Anhui, China

²Department of Oncology, The First Affiliated of Anhui Medical University, Hefei, Anhui, China

³Department of Neurology, The First Affiliated of Anhui Medical University, Hefei, Anhui, China

⁴Department of Pathology, The Affiliated Ruijin Hospital of Shanghai Jiaotong University, Shanghai, China

#These authors contributed equally to this work.

*Corresponding author: Ying Dai, dabora20051@hotmail.com

Article history

Received: 7 April 2024

Revised: 10 June 2024

Accepted: 14 June 2024

Published online: 4 July 2024

Keywords

Inflammatory myofibroblastic tumours
Central nervous system
Steroid therapy
ALK rearrangement
Cerebral tumours

Abstract

Introduction: Inflammatory myofibroblastic tumours (IMTs) are non-neoplastic lesions characterized by collagenous stroma and polyclonal mononuclear infiltrates. IMTs typically arise in the lung, retroperitoneum or abdominal region but rarely in the central nervous system (CNS). The primary therapeutic option is surgical resection, and other therapies are currently controversial.

Case report: We report a case of 23-year-old male ALK-negative cerebral IMT patient from Han population via steroid therapy. No relapse is observed at the follow-up visit.

Conclusion: These results support the role of internal medication and promote the use of personalized therapy in genome-profiled IMTs.

1. Introduction

Inflammatory myofibroblastic tumours (IMTs) are generally known as inflammatory pseudo-tumours (IPs). They are featured with non-neoplastic lesions with heterogeneous pathologies, including collagenous stroma, fibrous xanthoma, xanthomatous pseudotumours, plasma cell granulomas, plasma cell/histiocytoma complexes and pseudosarcomatous myofibroblastic proliferation [1]. The prevalence globally ranges from 0.04% to 0.7% regardless of gender and race [2]. The reported rate of mortality at 1 year was 4.4% (95% CI: 2.1%-8.9%) [3]. IMTs are mainly occur in lungs and infrequently in other organs such as the central nervous system (CNS) [4]. Neuropathology is mandatory for IP diagnosis, and surgical resection is recommended as the priority option [5]. Other alternative therapies, such as internal medication, are rarely discussed in publications. Here, we report one case of anaplastic lymphoma kinase (ALK)-negative CNS-IP successfully treated with steroids.

2. Case Presentation

A 23-year-old male patient presented with acute onset of weakness of the right limbs and dysarthria. He denied a family history of CNS disorders and tumour diseases. The neurological examination showed normal vital signs and normal muscle tension of the left limbs but decreased muscle tension and reinforced deep tendon reflexes of the right limbs in parallel with positive right

Babinski's reflex. Slurred speech, right haemiparesis (4/5 muscle strength diffusely) and hypoesthesia of the right limbs were also observed without negative meningeal signs or cognitive regression.

Blood biochemical tests revealed moderately enhanced antistreptolysin O (491 IU/ml) and C-reactive protein (4.97 mg/L). Levels of sexual hormones, tumour markers, thyroid hormone, erythrocyte sedimentation rate and cardiac enzymes were normal. Anti-leptospiral antibodies, antineutrophil cytoplasmic antibodies and antinuclear antibodies were negative. The electrocardiogram, electroencephalogram and CT angiography were also performed without any remarkable findings, whereas the cerebral CT scan revealed a low-density lesion adjacent to the left centrum semiovale and periventricular region. On MRI, the lesion was hypointense on T1-weighted images and hyperintense with perifocal oedema on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Figure 1A-1C). Biochemical tests of cerebrospinal fluid (CSF) revealed increased protein (0.56 g/L) and immunoglobulin (43 mg/L) levels. The patient was initially suspected of brain infarction and viral encephalitis. Unfortunately, paralysis of the right limbs (1/5 muscle strength) progressed immediately. When the biopsy pathologically indicated diffuse polymorph inflammatory infiltrate by foamy macrophages and lymphocytes (Figure 2A), his therapeutic management switched to 20 mg dexamethasone administered intravenously daily for two weeks until the muscle strength of the right limbs was restored to 4/5.

Fluorescence in situ hybridization (FISH) analysis thereafter indicated negativity for an ALK rearrangement (Figure 2B).

The patient relapsed with persistent dysarthria and haemiparesis of the right limbs two weeks later. He was then administered high-dose methylprednisolone (1000 mg/day intravenously for seven consecutive days) and

subsequent oral prednisone at 10 mg/day for three months until he completely recovered without any abnormal neurological symptoms. Cerebral MRI also confirmed the remarkable shrinkage of the lesion with perifocal oedema (Figure 1D-1F). At follow-up visits, he remained active without recurrence, consistent with the ongoing mass regression noted in cerebral MRI images (Figure 1G-1I).

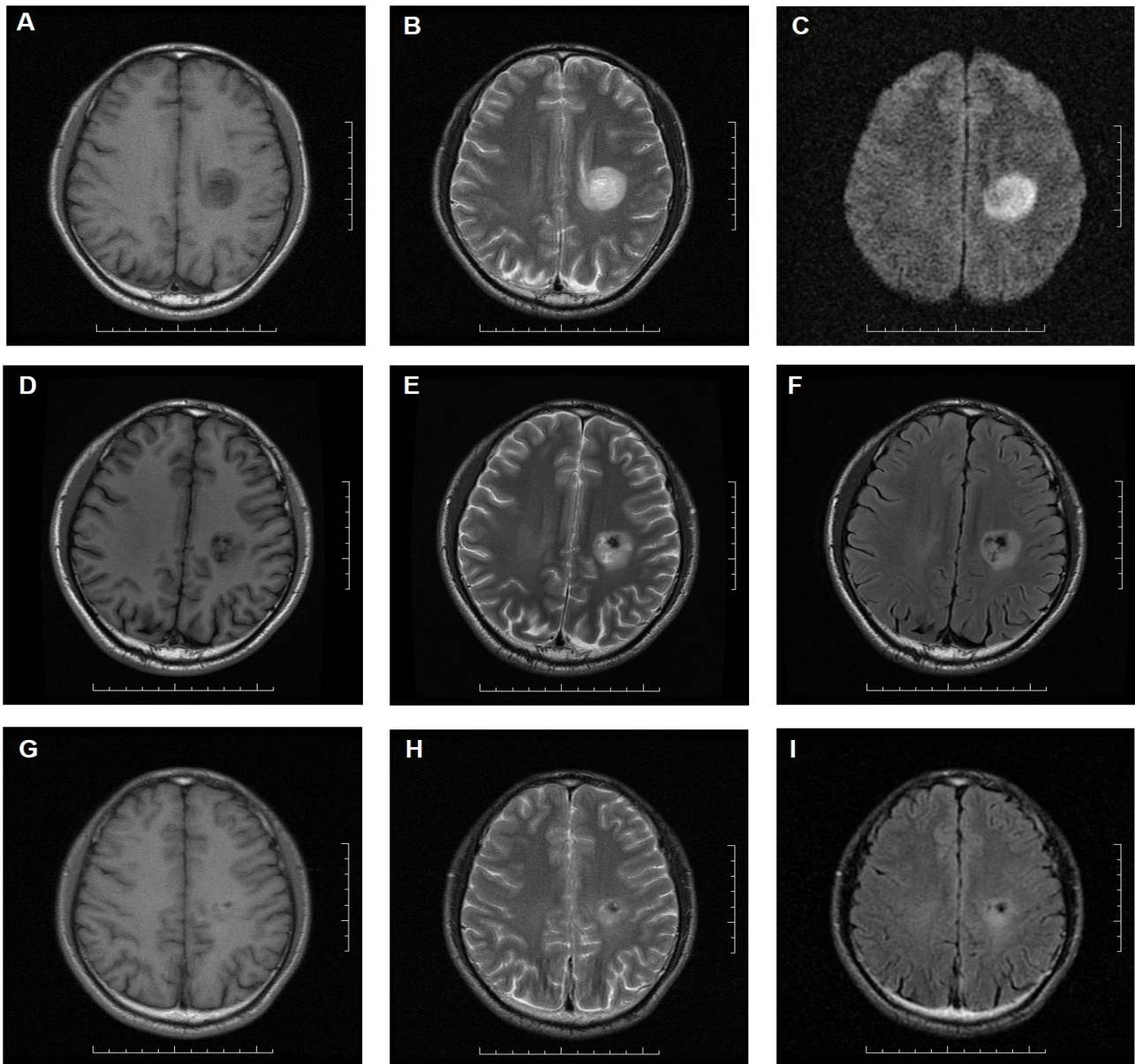


Figure 1. MRI image of the patient two days after onset. Axial T1-weighted sequence image showing a hypointense round lesion with perifocal oedema located in the left centrum semiovale and periventricular region (A). The mass is hyperintense on axial T2-weighted imaging (B). FLAIR sequence is utilized to improve the contrast of fluid and surrounding tissue, assisting the delineation. The hypointense mass is also shown on the FLAIR sequence image (C). The cerebral MRI images showed apparent shrinkage of the lesion on T1 (D), T2 (E) and DWI (F) images three months post steroid therapy. At the follow-up visit, ongoing shrinkage of the cerebral lesion was observed on T1 (G), T2 (H) and DWI (I) images.

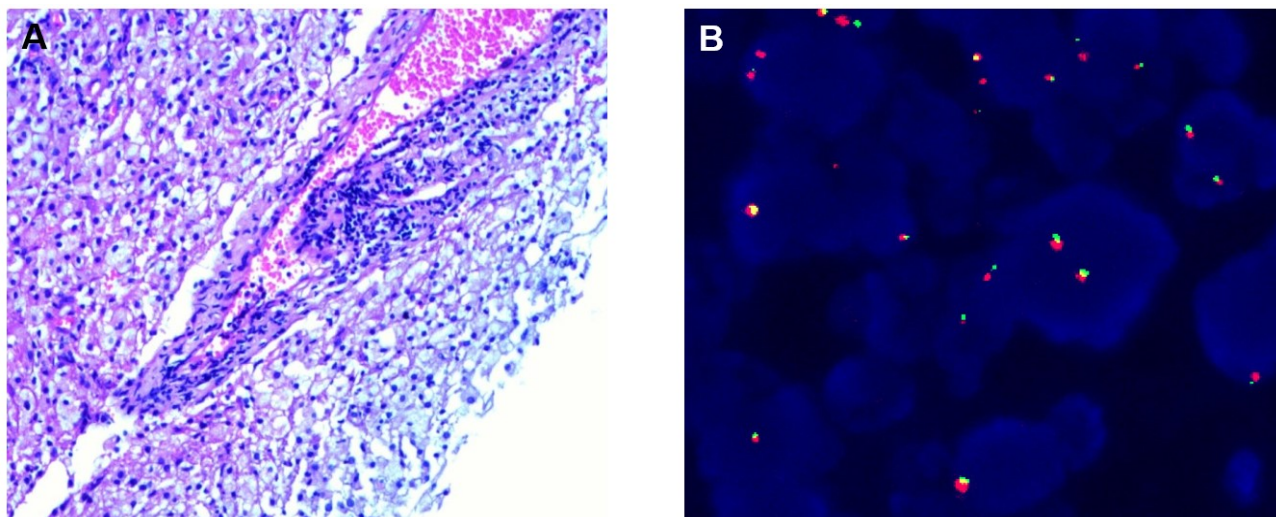


Figure 2. Microscopic features of IP (Hematoxylin & eosin staining and FISH staining). Within the entire microscopic field, the diffusive polymorph inflammatory infiltration was mainly composed of lipid-containing foamy macrophages, lymphocytes, and plasma cells. Perivascular aggregation of small lymphocytes and a few plasma cells was observed (magnification $\times 100$). The cytological atypia suggestive of atypical lymphoid proliferation and lymphoid follicles or granulomas were absent (A). FISH staining of the cerebral lesion sample indicated negativity for ALK rearrangement. ALK fusion was considered negative for rearrangement when red and green signals appeared adjacent, or yellow (fused) signals were seen (B).

3. Discussion and Conclusion

The early concept of IPs mostly consists of overwhelming inflammatory or reactive processes, but ALK gene rearrangements at chromosome 2p23 in a subset of IMT patients indicated additional neoplastic pathogenesis with poor prognosis [6,7].

Active autoimmune status, such as Crohn's disease, is reported to induce IPs in certain cases, accompanied by elevated levels of serum immunoglobulin [4,8]. The enrichment of IgG4 positive plasma cells was also reported in four cases with IP-CNS reported by Lui et al. [9]. Negative IgG4 expression was noted in IMT samples, which is consistent with its normal serum levels [10].

Our case proved the efficacy of steroids in ALK negative cerebral IPs, other than surgical resection as previously reported [11]. In one case of IP-CNS with dominant plasma cell infiltrate, steroid therapy demonstrated promising efficacy without aggravation or relapse in the 16-month follow-up [12]. The efficacy of steroid therapy with minor complications was also noted in one case of pulmonary IP [13]. Additionally, successful treatment with mycophenolate mofetil might elicit that immune inhibition (glucocorticoids and immune suppressors) potentially achieve a good response by attenuating the inflammatory activity of plasma- or inflammatory cell-infiltrated IPs [14].

Aberrant ALK expression (rearrangement or aneuploidy) has been described in approximately 50% of IMTs [15,16]. In our case, the negative ALK fusion of the cerebral lesion (Figure 2B) reflected its benign clinical behaviour and promising prognosis. ALK fusion includes ROS1, NTRK3 and RET genes [17,18]. Substantial evidence in vitro and in vivo indicated that

the ALK fusion protein, might induce malignant transformation related to mitogenic, antiapoptotic and potential DNA repair abilities [19]. It defined a subset of IMTs with tumour-like biological features that were also sensitive to ALK inhibition [20]. The success of crizotinib treatment was reported in at least half of ALK-positive IMT cases and also minor ALK-negative IMT patients [21-23]. Crizotinib was recommended as a treatment due to IMT patients' superior response to this ALK inhibitor. The positive ALK fusion in IMTs was distinctive nuclear membranous reactivity by IHC. In IMT cohort from one prospective study, ALK positive group was defined as over 15% of cells staining positive or showing gene rearrangement by IHC or FISH [23]. To date, no fusion protein was reported in ALK negative IMTs [18].

Previous studies indicated that the involvement of local inflammation in IMT pathogenesis, eliciting the therapeutic role of anti-inflammatory agents including steroids [24]. The reported intervention of steroids in IMTs is rare, therefore, the mechanistic studies are controversial. In some cases, the utilization of corticosteroids may promote IMT proliferation with resultant relapse [25]. For negative oncogene expression subgroups, steroid therapy alone or combined with surgical resection as adjuvant role is recommended for curative aims.

The current investigation of IMTs defined a series of gene aberrations including ALK, ATRX, FAT1, FCRL4, FOXO1, NUTM2B, PIK3CA, SMAD4, TP53 and ROS1 [26]. Other novel tyrosine kinase inhibitors including entrectinib and alectinib were also introduced with clinical efficacy in IMTs case. The unique neoplastic variety of IMTs necessitates conceptive strategies of personalized therapy originating from tumour disease, aiming to improve the prognosis of IMTs in future clinical practice [19,27].

List of Abbreviations

ALK	Anaplastic lymphoma kinase
CNS	Central nervous system
CSF	Cerebrospinal fluid
DWI	Diffusion weighted imaging
FISH	Fluorescence in situ histology
IMT	Inflammatory myofibroblastic tumour
IPs	Inflammatory pseudo-tumours

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Data and Material

Data generated during this study are included in this published article.

Funding

This work was supported by a grant from Fund of Anhui Institute of Translational Medicine (2023zhyx-C30). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing Interests

The authors declare no competing interests.

Author's Contributions

YJG and CJX collected and interpreted the clinical data. QD completed the pathology analysis. YD and LLW wrote the manuscript and graphical illustrations. All authors critically revised and approved the manuscript.

References

- [1] Hausler M, Schaade L, Ramaekers VT, Doenges M, Heimann G, et al. Inflammatory pseudotumors of the central nervous system: report of 3 cases and a literature review. *Human Pathology*. 2003, 34, 253-262. DOI: 10.1053/hupa.2003.35.
- [2] Surabhi VR, Chua S, Patel RP, Takahashi N, Lalwani N, et al. Inflammatory Myofibroblastic Tumors: Current Update. *Radiologic Clinics of North America*. 2016, 54, 553-563. DOI: 10.1016/j.rcl.2015.12.005.
- [3] Rich BS, Fishbein J, Lautz T, Rubalcava NS, Kartal T, et al. Inflammatory myofibroblastic tumor: A multi-institutional study from the Pediatric Surgical Oncology Research Collaborative. *International Journal of Cancer*. 2022, 151, 1059-1067. DOI: 10.1002/ijc.34132.
- [4] Derrey S, Charpentier C, Gerardin E, Langlois O, Touchais JY, et al. Inflammatory pseudotumor of the cerebellum in a patient with Crohn's disease. *World Neurosurgery*. 2012, 77(01), 201, e213-206. DOI: 10.1016/j.wneu.2011.05.034.
- [5] S al-Sarraj, J Wasserberg, R Bartlett, LR Bridges. Inflammatory pseudotumour of the central nervous system: clinicopathological study of one case and review of the literature. *British Journal of Neurosurgery* 1995, 9, 57-66. DOI: 10.1080/02688699550041764.
- [6] Fletcher CD. The evolving classification of soft tissue tumours—an update based on the new 2013 WHO classification. *Histopathology*. 2014, 64, 2-11. DOI: 10.1111/his.12267.
- [7] Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now? *Journal of Clinical Pathology*. 2008, 61, 428-437. DOI: 10.1136/jcp.2007.049387.
- [8] Dettmeyer R, Varchmin-Schultheiss K, Madea B. Intracranial plasma cell granuloma and homocystinuria. *Pathology, Research and Practice*. 1998, 194, 205-208. DOI: 10.1016/S0344-0338(98)80025-3.
- [9] Lui PC, Fan YS, Wong SS, Chan ANH, Wong G, et al. Inflammatory pseudotumors of the central nervous system. *Human Pathology*. 2009, 40, 1611-1617. DOI: 10.1016/j.humpath.2009.04.016.
- [10] Kim SA, Lee SR, Huh J, Shen SS, Ro JY. IgG4-associated inflammatory pseudotumor of ureter: clinicopathologic and immunohistochemical study of 3 cases. *Human Pathology*. 2011, 42, 1178-1184. DOI: 10.1016/j.humpath.2010.03.011.
- [11] Wang X, Chen Y, Wu X, Zhang HL. Intracranial Inflammatory Myofibroblastic Tumor with Negative Expression of Anaplastic Lymphoma Kinase: A Case Report and Review of the Literature. *World Neurosurgery*. 2019, 125, 117-122. 2019/02/09. DOI: 10.1016/j.wneu.2019.01.155.
- [12] Carswell C, Chataway J. The successful long-term management of an intracranial inflammatory myofibroblastic tumor with corticosteroids. *Clinical Neurology and Neurosurgery*. 2012, 114, 77-79. 2011/09/06. DOI: 10.1016/j.clineuro.2011.07.026.
- [13] Yi E, Aubry MC. Pulmonary pseudoneoplasms. *Archives of Pathology & Laboratory Medicine*. 2010, 134, 417-426. DOI: 10.1043/1543-2165-134.3.417.
- [14] Moss HE, Mejico LJ, de la Roza G, Coyne TM, Galetta SL, et al. IgG4-related inflammatory pseudotumor of the central nervous system responsive to mycophenolate mofetil. *Journal of the Neurological Sciences*. 2012, 318, 31-35. DOI: 10.1016/j.jns.2012.04.010.
- [15] Coffin CM, Patel A, Perkins S, Elenitoba-Johnson KS, Perlman E, et al. ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. *Modern Pathology*. 2001, 14, 569-576. DOI: 10.1038/modpathol.3880352.
- [16] Griffin CA, Hawkins AL, Dvorak C, Henkle C, Ellingham T, et al. Recurrent involvement of 2p23 in inflammatory myofibroblastic tumors. *Cancer Research*. 1999, 59, 2776-2780. PMID: 10383129.
- [17] Chang JC, Zhang L, Drilon AE, Chi P, Alaggio R, et al. Expanding the Molecular Characterization of Thoracic Inflammatory Myofibroblastic Tumors beyond ALK Gene Rearrangements. *Journal of Thoracic Oncology*. 2019, 14, 825-834. DOI: 10.1016/j.jtho.2018.12.003.
- [18] Lovly CM, Gupta A, Lipson D, Otto G, Brennan T, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. *Cancer Discovery*. 2014, 4, 889-895. DOI:

- 10.1158/2159-8290.CD-14-0377.
- [19] Dai Y, Wei Q, Schwager C, Moustafa M, Zhou C, et al. Synergistic effects of crizotinib and radiotherapy in experimental EML4-ALK fusion positive lung cancer. *Radiotherapy and Oncology*. 2015, 114, 173-181. DOI: 10.1016/j.radonc.2014.12.009.
- [20] Giuriato S, Faumont N, Bousquet E, Foisseau M, Bibonne A, et al. Development of a conditional bioluminescent transplant model for TPM3-ALK-induced tumorigenesis as a tool to validate ALK-dependent cancer targeted therapy. *Cancer Biology & Therapy*. 2007, 6, 1318-1323.
- [21] Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *The New England Journal of Medicine*. 2010, 363, 1727-1733. DOI: 10.1056/NEJMoa1007056.
- [22] Gambacorti-Passerini C, Orlov S, Zhang L, Braiteh F, Huang HQ, et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. *American Journal of Hematology*. 2018, 93, 607-614. DOI: 10.1002/ajh.25043.
- [23] Schoffski P, Sufliarsky J, Gelderblom H, Blay JY, Strauss SJ, et al. Crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumours with and without anaplastic lymphoma kinase gene alterations (European Organisation for Research and Treatment of Cancer 90101 CREATE): a multicentre, single-drug, prospective, non-randomised phase 2 trial. *The Lancet Respiratory Medicine*. 2018, 6, 431-441. DOI: 10.1016/S2213-2600(18)30116-4.
- [24] Watanabe R, Ano S, Kikuchi N, Shigemasa R, Kondo Y, et al. Inflammatory myofibroblastic tumor directly invading the right first rib treated with oral steroids: a case report. *BMC Pulmonary Medicine*. 2024, 24, 67. DOI: 10.1186/s12890-024-02873-6.
- [25] Jiang JY, Comsa M, Wong VCK, Mansberg R. Steroid responsive inflammatory myofibroblastic tumor of the lung evaluated by FDG PET/CT imaging. *Radiology Case Reports*. 2022, 17, 907-910. DOI: 10.1016/j.radcr.2021.11.049.
- [26] Gros L, Dei Tos AP, Jones RL, Digkila A. Inflammatory Myofibroblastic Tumour: State of the Art. *Cancers (Basel)*. 2022, 14. DOI: 10.3390/cancers14153662.
- [27] Huber PE, Bischof M, Jenne J, Heiland S, Peschke P, et al. Trimodal cancer treatment: beneficial effects of combined antiangiogenesis, radiation, and chemotherapy. *Cancer Research*. 2005, 65, 3643-3655. DOI: 10.1158/0008-5472.CAN-04-1668.