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TRIMODALITY APPROACH WITH NEOADJUVANT CRIZOTINIB, CORTICOSTEROID AND RADIOTHERAPY FOR UNRESECTABLE GIANT MYOFIBROBLASTIC TUMOR OF THE LUNG IN A YOUNG FEMALE

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Introduction - Purpose : Inflammatory myofibroblastic tumor (IMT) is a rare neoplasm characterized by spindle-cell proliferation with an inflammatory infiltrate which expresses cyclooxygenase-2 (COX-2) and carries rearrangements of the anaplastic lymphoma kinase (ALK). Although primary treatment is surgery, additional treatment options are needed when the surgical intervention is not feasible. It may be an alternative, effective and more tolerabl way to treat with anti-inflamatory agents and ALK inhibitors in ALK rearranged group of patients

Methods - Tools : Inflammatory myofibroblastic tumors (IMTs) belong to an intermediate group of soft-tissue tumors and first reported in 1990 by Pettinato et al (1). It is difficult to differantiate clinically IMTs from malignant tumors and infections. IMTs are occur primarily during the first two decades and most commonly detected in the lung, retroperitoneum and abdomino-pelvic area (2). Although initially thought to be a benign process, subsequent studies have shown IMT to be neoplastic with the ability to recur locally and metastasize (2). At present no standard treatment has been established except surgery. Because of some tumors are not amenable to surgical excision, several treatment modalities such as chemotherapy, radiation and anti-inflammatory therapy have been used alone or as an adjuvant therapy with surgery. Although anti inflamatory drug therapy has been showed clinically effective in recently published case based reports, no clinical trials have shown clinical efficacy. Recently, the relationship between IMTs and ALK gene rearrangements has been investigated. The presence of ALK rearragement was found in 50% of IMT cases and molecular targeted inhibitors have proven effective for patients with this chromosomal rearragements in case base reports (3) . We present here a giant unresectable IMT case of lung treated with a combination of anti-inflamator and targeted inhibitor drug treatment .

Findings : The patient was a 26-year-old female who presented with dyspnea and atypical chest pain. Chest CT and 18-F FDG PET- CT scanning revealed a locally aggressive primary tumour with no distant metastases. (figure a-c) A diagnosis of IMT was made on the basis of histologic analysis of the tissue extracted by video-asisted thoracic surgery (VATS) . The tumor cells were focally positive for muscle-specific actin, vimentin and p53. All other markers were negative, including CD34, CD35, SMA, S-100, CD68 and CD117. The cellular morphologic features and negativity for these markers ruled out entities that mimic IMT such as other soft tissue sarcomas and spindle-cell melanoma. ALK immunohistochemical analysis was positive and FISH studies revealed ALK gene rearrangement. Due to unresectability of the tumor; the patient began to recieve prednisone and ibuprofen. Intensity modulated Radiotherapy (IMRT) was planned concurrently. The patient had symptomatic relief. Post radiotherapy Chest CT was performed before surgery. CT scanning showed partial response according to Response Evaluation Criteria in Solid Tumors (RECIST). The tumor was still unresectable for the thoracic surgery. After meeting eligibility criteria and providing written informed consent, the patient began to received crizotinib at a dose of 250 mg twice daily. The patient stil receives crizotinib treatment; despite clinical response, radiological response evalution have not yet been obtained.

Discussion : IMT is a rare neoplasm of intermediate biological potential, which is characterized by spindle-cell proliferation with an inflammatory infiltrate (4). It typically arises in the lung and

retroperitoneum (2). Several histologic patterns of IMT have been described, including those with compact spindle cell, myxoid-vascular, and hypocellular fibrous morphologic features. (2). Infrequently, IMT will be locally invasive or has rapid recurrence after surgery and rarely may even transform into a true sarcoma (5). It is debatable whether it is a tumor or inflammatory lesion. Primary treatment of IMT is surgical excision when possible. In cases where surgical resection is not possible, or with recurrent disease after resection, additional treatment options are needed. Radiotherapy, chemotherapy, NSAIDs, steroids, antibiotics have been shown to be effective in many case based studies (6-9) . None has been found to be consistently effective and to date, standardized therapy has not been established. In addition, genetic markers have been found in some lesions, suggesting that these may play a role in the pathogenesis or the clinical course of the disease (10, 11). A recent case report suggested that testing for the ALK gene rearrangement in IMT may be helpful in determining the best chemotherapy for metastatic lesions (12). There have been several previous reports of successful treatment of ALK positive IMTs with the ALK inhibitors crizotinib and ceritinib (13-16). Anti-inflammatory therapy for IMT was first discovered by hakozaki et al (17) based on pathophysiology of the disease. Other reports associated with therapy of IMT have been shown in subsequent studies (18). Although the mechanism is unknown, it is thought to be releated to the ability of anti-inflammatory drugs, such as COX-2 inhibitors, to block the mediators of angiogenesis including Vascular endothelial growth factor (VEGF). An increased level of pro-inflammatory cytokines, such as interleukin-6 and nuclear factor kappa B are both commonly detected in clinical manifestations of IMTs (18). We aimed to increase the chances of surgical resectability by using ALK inhibitor treatment together with anti-inflammatory treatment in the case of ALK positive IMT which is unresectable despite radiotherapy treatment .Good clinical response was obtained and we hope that we will get better results after radiological evaluation. To the best of our knowledge, this is the first published case report on preoperative trimodality treatment with crizotinib, steroids and radiotherapy for IMT of the lung. The long-term prognosis of this patient is uncertain since the tumor has not been resected. Neverthless, this kind of treatment modalities may be appropriate when surgical excision is not feasible. In the future, subsequent development of targeted therapies may result in successful management of malignant IMTs. REFERENCES 1. Pettinato, Guido, et al. "Inflammatory myofibroblastic tumor (plasma cell granuloma): clinicopathologic study of 20 cases with immunohistochemical and ultrastructural observations." American Journal of Clinical Pathology 94.5 (1990): 538-546. 2. Coffin, Cheryl M., et al. "Extrapulmonary Inflammatory Myofibroblastic Tumor (Inflammatory Pseudotumor) A Clinicopathologic and Immunohistochemical Study of 84 Cases." The American journal of surgical pathology 19.8 (1995): 859-872. 3. Giuriato, Sylvie, 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 6.8 (2007): 1324-1329. 4. Chen, Ming, et al. "Partial response to chemotherapy in a patient with retroperitoneal inflammatory myofibroblastic tumor." Molecular and clinical oncology 5.4 (2016): 463-466. 5. Donner, Ludvik R., Raymond A. Trompler, and Raleigh R. White. "Progression of inflammatory myofibroblastic tumor (inflammatory pseudotumor) or soft tissue into sarcoma after several recurrences." Human pathology 27.10 (1996): 1095-1098. 6. Johnson, Kevin, et al. "Successful treatment of recurrent pediatric inflammatory myofibroblastic tumor in a single patient with a novel chemotherapeutic regimen containing celecoxib." Journal of pediatric hematology/oncology 35.5 (2013): 414-416. 7. Bagri, PUNEET KUMAR, et al. "Successful treatment of inflammatory myofibroblastic tumor by surgical resection and radiotherapy: A case report." Int. J. Radiat. Res 12.4 (2014): 387-390. 8. Lee, Min Hee, et al. "Bilateral multiple inflammatory myofibroblastic tumors of the lung successfully treated with corticosteroids." Lung 189.5 (2011): 433. 9. Ghani, Sofia, et al. "Pneumonectomy-Sparing NSAID Therapy for Pulmonary Inflammatory Myofibroblastic Tumor." Journal of thoracic oncology 10.9 (2015): e89-e90. 10. Snyder, Cynthia S., et al. "Clonal changes in inflammatory pseudotumor of the lung. A case report." Cancer 76.9 (1995): 1545-1549. 11. Biselli, Roberto, et al. "Inflammatory myofibroblastic tumor (inflammatory pseudotumor): DNA flow cytometric analysis of nine pediatric cases." Cancer77.4 (1996): 778-784. 12. Butrynski, James E., et al. "Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor." New England Journal of Medicine 363.18 (2010): 1727-1733. 13. Tothova, Zuzana, and Andrew J. Wagner. "Anaplastic lymphoma kinase-directed therapy in inflammatory myofibroblastic tumors." Current opinion in oncology 24.4 (2012): 409-413. 14. Jacob, Sanjivini V., et al. "An unusual case of

systemic inflammatory myofibroblastic tumor with successful treatment with ALK-inhibitor." Case reports in pathology 2014 (2014). 15. Mansfield, A. S., et al. "Chromoplectic TPM3–ALK rearrangement in a patient with inflammatory myofibroblastic tumor who responded to ceritinib after progression on crizotinib." Annals of Oncology (2016): mdw405. 16. Liu, Qiuyu, et al. "Epithelioid inflammatory myofibroblastic sarcoma treated with ALK inhibitor: a case report and review of literature." International journal of clinical and experimental pathology 8.11 (2015): 15328. 17. Hakozaki, Y. "Improvement of inflammatory pseudotumor of the liver after nonsteroidal anti-inflammatory agent therapy." Am J Gastroenterol 88 (1993): 1121-1122. 18. Fukano, Reiji, et al. "Time lag between the increase of IL-6 with fever and NF-?B activation in the peripheral blood in inflammatory myofibroblastic tumor." Cytokine 44.2 (2008): 293-297.

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Figure a-b-c: CT and 18-F FDG PET-CT image of IMT localized in left anterior lung