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CASE REPORT

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Histiocyte-rich ROS1-rearranged inflammatory myofibroblastic tumour of the trachea: A rare neoplasm presenting with asthma-like symptoms

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Abstract

Inflammatory myofibroblastic tumour is a rare tumour. We present an atypical case of Inflammatory myofibroblastic tumour which was trachea in location, histocyte rich and ROS1 rearranged. The patient presented with upper airway obstruction, which was an asthma mimic. The tumour demonstrated rapid recurrence after mechanical coring, which subsequently controlled with radiotherapy.

KEYWORDS
inflammatory myofibroblastic tumour, ROS1 translocation

INTRODUCTION

Inflammatory myofibroblastic tumour is classically myofibroblast-rich and ALK rearranged. We describe a middle-aged woman with atypical inflammatory myofibroblastic tumour.

CASE REPORT

A 49-year-old lady presented in July 2022 with dyspnea and productive cough for 2 weeks. Physical examination showed stridor and expiratory wheeze. Chest x-ray showed clear lung fields. Patient was initially treated as asthma by empirical antibiotic and systemic steroid. Flexible laryngoscopy by otolaryngologist showed clear airway down to the vocal cord. Patient was discharged when her recorded peak expiratory flow had improved. A scheduled lung function test later demonstrated an Empey index of 14.5 and expiratory disproportion index of 87, with flow volume loop suspicious of fixed upper airway obstruction (Figure 1).

She was readmitted 1 week later to hospital for persistent dyspnea. Arterial blood gas revealed compensated type 2 respiratory failure. Contrast computed tomography (CT) of neck and thorax identified a $2 \times 2 \times 1.2$ cm enhancing polypoid nodule at the cervical trachea, located 2.6 cm inferior to the vocal cords (Figure 2). The nodule arose from the left posterolateral tracheal wall causing more than 70% of tracheal luminal stenosis. Rigid bronchoscopy found a large fleshy tumour in the trachea 3 cm inferior to the vocal cord and causing 80% luminal obstruction. Mechanical coring was performed.

Microscopic examination of the biopsy showed a submucosal histiocyte-rich lesion, with neoplastic spindle cells

Chin Tong Kwok and Jason Cheuk Ho Tsang have equal contribution.

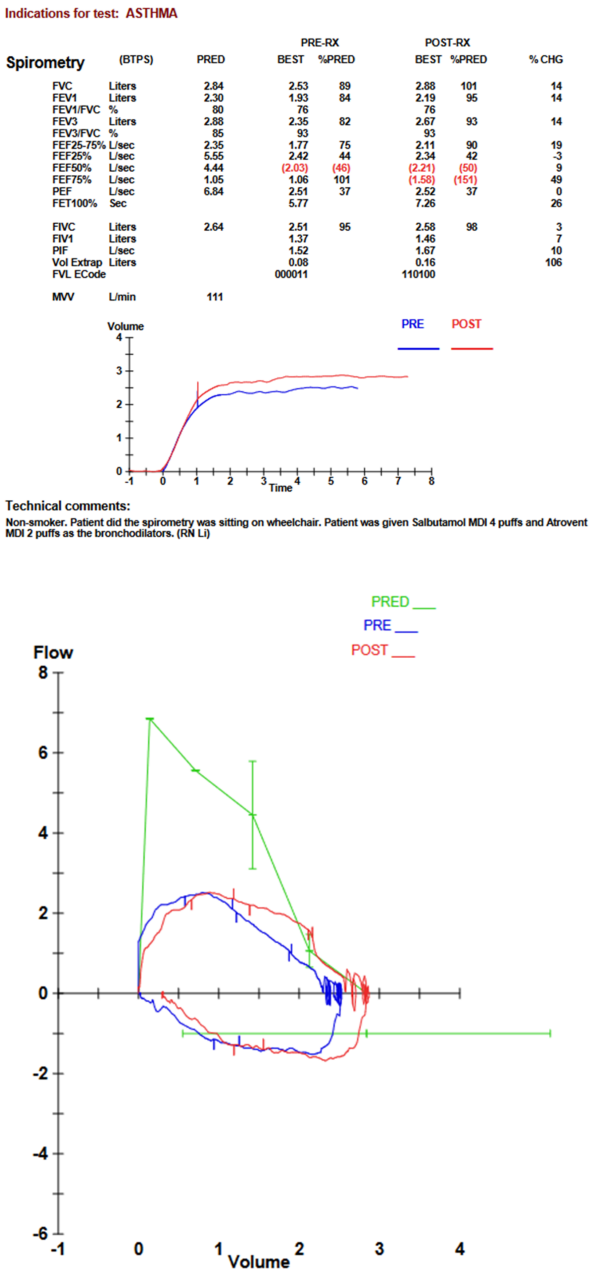

FIGURE 1 Spirometry demonstrated the typical fixed upper airway obstruction pattern on flow volume loop: Very low peak expiratory flow and normal forced expiratory volume in 1 s.

arranged in fascicles, intimately associated with mixed populations of plasma cells, lymphocytes and abundant histiocytes (Figure 3). The neoplastic spindle cells possessed plump vesicular nuclei, distinct nucleoli and amphophilic cytoplasm. Mitotic activity was readily identified and tumour necrosis was focally seen. Immunostaining for histiocytic markers (CD163 and CD68) showed apparent diffuse strong staining in tumour tissue, but additional immunostaining of PU.1, a transcription factor with nuclear immunostaining pattern in histiocytes, indicated that the neoplastic spindle cells are not histiocytic in nature (Figure 4). The spindle cells showed patchy smooth-muscle actin staining and diffuse strong cytoplasmic expression of ROS1, while pan-cytokeratin (MNF116), CAM5.2, p40, pan-TRK, ALK, BRAFV600E(VE1), S100 and SOX10 were negative. Fluorescence in-situ hybridization confirmed presence of *ROS1* gene rearrangement using breakapart probes. The final diagnosis was *ROS1*-rearranged inflammatory myofibroblastic tumour (IMT).

Follow-up flexible bronchoscopy performed 3 weeks after mechanical coring showed residual tumour growth (Figure 5). Surveillance bronchoscopy 3 months later showed tumour recurrence with 90% obstruction of the tracheal lumen, and mechanical coring was repeated. CT in the subsequent week showed a 1.1 cm trachea wall soft tissue lesion, raising suspicion for residual disease. There was no other systemic disease. Bronchoscopy was repeated showing a small residual tumour. In view of repeated locally recurrent disease, treatment to reduce incidence of regrowth was indicated. Excision was deemed not suitable due to the extension of the tumour to the oesophagus and thyroid. Patient opted for conformal RT as the non-invasive means for disease control. Patient was set up in supine position with extended neck and immobilized in thermoplastic shell. The RT prescription was 2 greys (Gy) per fraction, 5 fractions per week, up to total of 50 Gy given over 5 weeks. The treatment was well tolerated with no significant acute toxicities. Progress CT performed at 8 months post-RT showed slight shrinkage of the residual tumour. Bronchoscopy performed at 2, 5, and 10 months after RT showed that the residual tumour remained stable with no further rebound.

DISCUSSION

This case highlighted the importance of identifying asthma mimics. An early spirometry can help screening cases that will need emergent attention. Apart from the classical flow-volume-loop pattern, Empey index and Expiratory disproportion index help to identify upper airway obstruction. Empey index refers to the forced expiratory velocity in 1 s (FEV1) (in mL) over peak expiratory flow (PEF) (in litre per minute). Empey index greater than 10 is suggestive of upper airway obstruction.[1] Expiratory disproportion index refers to FEV1 (in litre) over PEF (in litre per second) multiplied by 100. An index greater than 50 signifies laryngotracheal obstruction.[2] This index is directly proportional to the severity of airway obstruction: if the index is greater than 75, emergent treatment is warranted.[2] In this case, an expiratory disproportion index of 87 would alert the physician to arrange an urgent bronchoscopy.

Inflammatory myofibroblastic tumour is a rare tumour of intermediate malignancy, primarily affecting children and young adults. It is characterized by myofibroblastic proliferation in the background of prominent lymphoplasmacytic infiltrate. The current case further shows several unusual pathological features, namely tracheal localization,

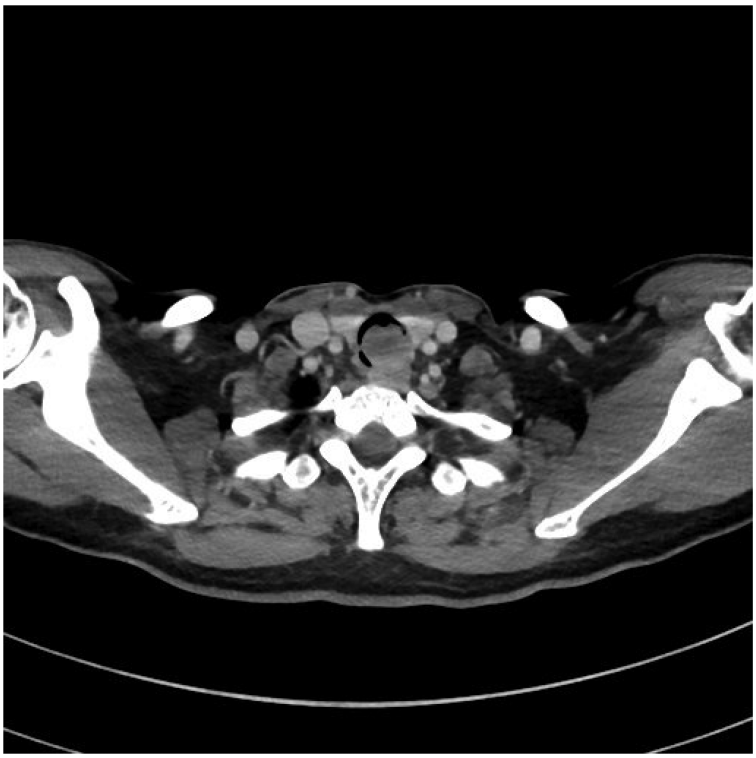

FIGURE 2 Contrast computed tomography of neck and thorax demonstrated a tracheal tumour causing 70% stenosis.

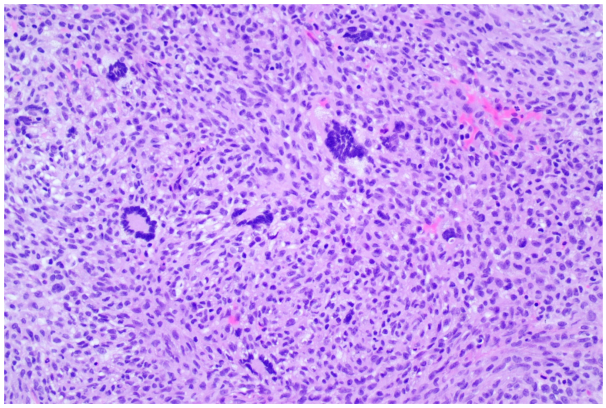

FIGURE 3 Presence of Touton-type multinucleated histiocytes in the tumour (200× magnification).

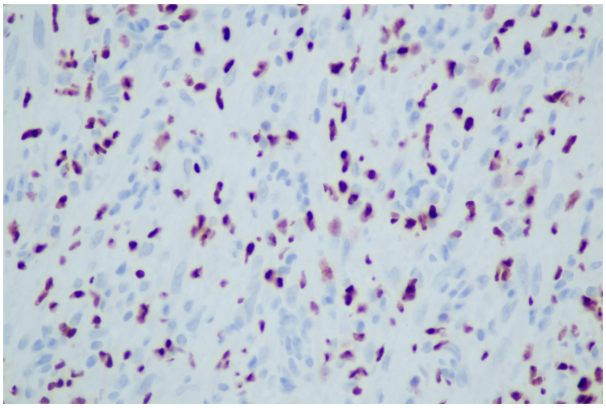

FIGURE 4 Nuclei of histiocytes can be highlighted by PU.1 immunostaining, which provides more intuitive identification of the non-histiocytic nature of the neoplastic cells in the background (400× magnification).

histiocyte-rich histological pattern and *ROS1* gene rearrangement. In many areas, the neoplastic myofibroblasts are obscured by histiocytes, mimicking a histiocytic neoplasm. Furthermore, multinucleated Touton giant cells, which are more commonly seen in benign histiocytic lesions, such as juvenile xanthogranuloma or dermatofibroma, are seen in foci in this tumour. The more typical fascicular proliferation of myofibroblastic spindle cells is only observed in focal areas. This tumour harbours *ROS1* gene rearrangement, which is much less common than *ALK* gene earrangement.[3] This case illustrates the need for comprehensive molecular assessment in the diagnosis of inflammatory myofibroblastic tumour. The presence of *ROS1* gene rearrangement carries therapeutic implication and predicts response to targeted ROS1 inhibitor.[4]

IMTs can be locally aggressive and have high recurrence rate after excision, but they seldom metastasize.[5] Surgical resection is the mainstay of treatment. Chemotherapy or targeted therapy can be considered if surgery is not feasible or margin is involved. For chemotherapy, vinblastine and methotrexate can be used.[5] More than half of IMTs harbour *ALK* rearrangement, but rare cases show rearrangements of ROS1, PDGFRβ, RET and NTRK genes. In view of the molecular characteristics of IMT, tyrosine kinase

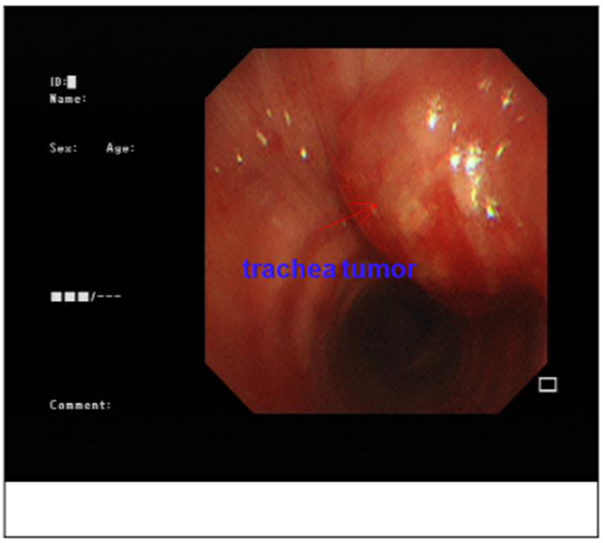

FIGURE 5 Follow-up flexible bronchoscopy performed after mechanical coring showed residual tumour.

inhibitors and novel targeted agents against these mutations are evolving therapeutics for management of unresectable or residual disease. However, prolonged use of targeted agents for control of localized disease may expose patients to various systemic adverse effects. Treatment with radiotherapy offers the advantage of salvaging local recurrence while sparing the patient from systemic toxicities. Similar to the published cases with tumours rich in lymphoplasmacytic cells, our case demonstrated favourable response to radiotherapy.

AUTHOR CONTRIBUTIONS

Concept or design: Chin Tong Kwok. *Acquisition of data*: Chin Tong Kwok, Jason Cheuk Ho Tsang. *Analysis or interpretation of data*: Chin Tong Kwok, Jason Cheuk Ho Tsang. *Drafting of the article*: Chin Tong Kwok, Jason Cheuk Ho Tsang, Mary Lam, Sandy Sze Ki Ho. *Critical revision for important intellectual content*: Chin Tong Kwok, Jason Cheuk Ho Tsang, Mary Lam, Sandy Sze Ki Ho, Chi Sum Yuen, Yiu Cheong Yeung. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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