Inflammatory myofibroblastic tumor of the upper airways harboring a new TRAF3-ALK fusion transcript.

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Abstract

Inflammatory myofibroblastic tumor (IMT) is a rare disease that mainly involves the lung and the abdomen with an intermediate clinical course but a recurrence rate between 15-30%. Radical surgery represents the golden standard of treatment, while chemotherapy and radiotherapy are considered for unresectable lesions. The identification of ALK translocations in IMT opened the option for the use of target therapies1. Indeed, the ALK inhibitors have changed the treatment approach for aggressive lesions, improving the prognosis. Intraluminal upper way IMT is extremely rare and represents a medical challenge. We reported an endotracheal IMT case presenting a before unknown TRAF3-ALK fusion transcript.

Brief Report (PBC)

TITLE

Inflammatory myofibroblastic tumor of the upper airways harboring a new ALK fusion transcript.

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Running title: inflammatory myofibroblastic tumor in children

KEYWORDS

Inflammatory myofibroblastic tumor, children, ALK inhibitors, crizotinib

ABSTRACT

Inflammatory myofibroblastic tumor (IMT) is a rare disease that mainly involves the lung and the abdomen with an intermediate clinical course but a recurrence rate between 15-30%.

Radical surgery represents the golden standard of treatment, while chemotherapy and radiotherapy are considered for unresectable lesions. The identification of ALK translocations in IMT opened the option for the use of target therapies[1]. Indeed, the ALK inhibitors have changed the treatment approach for aggressive lesions, improving the prognosis.

Intraluminal upper way IMT is extremely rare and represents a medical challenge.

We reported an endotracheal IMT case presenting a before unknown TRAF3-ALK fusion transcript.

ABBREVIATIONS

IMT Inflammatory myofibroblastic tumor

ALK Anaplastic lymphoma kinase

CT Computer tomography

PICU Pediatric intensive care unit

EORTC European Organization for Research and Treatment for Cancer

BACKGROUND

Inflammatory myofibroblastic tumor (IMT) is a rare disease with a first peak before the age of 20 years and a second one between 50 e 60 years[2]. It was first described in 1973 as a primary lung tumor[3] and since then, both lung and multiple extra pulmonary manifestations have been reported[4,5,6].

The etiology still remains unknown but probably is related to an abnormal inflammatory response due to an immunological trigger at different antigens.

A wide spectrum of clinical and biological behavior is described, ranging from benign proliferations to intermediate–locally aggressive, intermediate–rarely metastasizing and malignant tumors.

The possibility of slow progression into a sarcoma has been reported[7] as metastatic spread[8].The lung, soft tissues and abdomen are the most involved primary sites. Surgery represents the stand-alone treatment for IMT, with a 91% 5-year disease free survival[8]. Chemotherapy was considered for unresectable, multifocal or metastatic disease with a response rate of 50-60%. Radiotherapy is usually reserved for a palliative approach, alone or in combination with chemotherapy[9,10]. Steroids or non-steroid anti-inflammatory drugs are also been considered[7].

The ALK translocations are identified in IMT, representing an oncogenic trigger; the ALK inhibitors have changed the treatment approach for unresectable/metastatic and/or recurrent lesions, improving the prognosis and overall survival[1].

The endobronchial or endotracheal localization is extremely rare but with a challenging approach considering the efficacy of focal treatment.

We reported on an endotracheal IMT case with a never yet reported TRAF3-ALK fusion transcript, and a brief review of published cases.

CASE PRESENTATION

A six-year-old girl was admitted to a general hospital with fever, persistent cough and dyspnea. No episodes of recurrent respiratory infections were reported. Blood tests revealed only an increase of C-reactive protein 9.67 mg/dl (range 0-0.5), Chest X-ray showed a bilateral pneumonia. Oxygen therapy plus antibiotic therapy and steroids were started without any improvement and needing for invasive respiratory support

A Computed Tomography (CT) scan confirmed multiple pulmonary consolidations on both lobes. COVID molecular nasopharyngeal test was negative. MA solid-like parietal protrusion floating in the tracheal lumen (approximately 12x8 mm) was detected. All microbiological tests were negative. Diagnostic work-up included a fibroscopy with bronchiolar-alveolar washing and biopsy of the endotracheal mass. Patient was referred to our hospital.

The pathology revealed an ulcerated mucosa with an underlying proliferation of bland spindle to stellate-shaped cells in a myxoid stroma associated with a mild inflammatory infiltrate including lymphocytes, scattered plasma cells and histiocytes. Immunohystochemical stains showed positivity for vimentin and smooth muscle actin while ALK1, ALKp80, desmin, myogenin, cytocheratin CAM5.2, CD45, CD31, S100, EMA and MUC4 were all negative. An unbalanced rearrangement of ALK (exons 10-20), showing TRAF3-ALK fusion transcript was found. Finally, a diagnosis of IMT was rendered. The surgery was postponed considering the high risk of bleeding, mutilation and life-threatening complications. Crizotinib was started at 165 mg/mq/dose twice daily for 21 days/course with a rapid improvement and weaning from mechanical respiratory support confirmed at endotracheal fibroscopy demonstrating a partial response (fig.1). The child was discharged from pediatric intensive care unit (PICU). After two-week treatment, a new CT scan showed a 70% reduction of the mass achieving the best response after 4 weeks from Crizotinib. No mild or severe treatment side effect were observed.

At the time of the last follow-up, after eight months of therapy, she is still on treatment. The patient is in good condition and achieved a complete response (fig 2).

DISCUSSION

We described a rare case of pediatric endotracheal IMT with a not-previously reported ALK fusion transcript successfully treated with ALK inhibitor.

Since the first report in 1989[11]; upper airways IMT- including trachea and main bronchus- have been reported in 16 patients. The median age at diagnosis was 9 years, with a male/female ratio of 1. All the patients have a histological diagnosis of IMT, but ALK status was reported in only five cases. Treatment strategy are listed in Supplemental Table 1[11-25]. Aggressive surgery was the primary approach considering the critical condition in more than 50% of patients. Moreover, some reports were published before 2008, when surgery and chemotherapy were recommended, but ALK-inhibitors trials were not yet developed.

In our case, a prompt diagnosis with molecular characterization was achieved. Considering the IMT diagnosis with a TRAF3-ALK fusion transcript, Crizotinib was suddenly started with a rapid recovery and impressive lesion reduction.

The Crizotinib is a small molecule targeting multiples tyrosine-kinases such as ALK, ROS, ROS1, MET, and interferes with ALK-pathway, blocking oncogenic proliferation[26]. It was approved firstly for advanced ALK-positive or ROS1-positive non-small cells lung cancer[27].

ALK fusions were detected also in neuroblastoma, rhabdomyosarcoma, anaplastic large-cell lymphoma, and IMT[1,28]; several trials investigating the safety and efficacy in these subsets were run.

In 2010, in a phase I/II clinical trial, Butrynski et al. reported a brilliant response to Crizotinib of ALK-positive IMT[29]. The COG phase I/II trial on pediatric anaplastic large cell lymphoma and IMT treated

with Crizotinib reported five complete and seven partial responses among fourteen pediatric patients, with an 86% response rate[30].

Furthermore, a phase II pediatric clinical trial by the EORTC reported an objective response in 50% of patients, with mild adverse events in among 10% of patients (more frequently nausea, fatigue, blurred vision and diarrhea, without any severe or life-threating adverse events)[31].

Recently, further reports studied others ALK inhibitors, like Alectinib and Ceritinib[32].

Craig et al. described 29 patients affected by ALK-positive IMT who underwent therapy with an ALK-inhibitor. Twelve experienced complete response (41.3%), fourteen a partial response (48.3%) and three (7%) stable disease. Two (7%) had recurrence at the stop-therapy; anyway, they achieved a second complete response after restarting the therapy[33].

The TRAF3-ALK fusion transcript (involving exons 10 and 20) has never been reported before in literature; in IMT, more than 10 different genes have been identified as ALK fusion partners, including TPM3/4, RANBP2, TFG, CARS, ATIC LMNA, PRKAR1A, CLTC, FN1, SEC31A, and EML4[34]. ALK status is known to correlate with survival[35].

Rarely, IMT can harbor mutations of ROS1, PDGFRb, NTRK or RET, needing further studies to correlate with clinical presentations and outcome[36].

In conclusion, the endotracheal IMT diagnosis, even if rare, should be considered in children with respiratory symptoms, radiological atypical findings and no response to medical treatment.

The standard approach with primary huge surgery may be delayed, considering the high risk of life-threatening complications related to anatomical localization, and a conservative approach should be instead considered, according also to recent molecular findings and the ALK inhibitors option.

This report stress the role of target therapy, underlying their rapid clinical results, with a quickly control of respiratory distress and without a demolitive surgical approach.

ETHICS STATEMENT

The authors state that written informed consent was obtained from the parents of the patient for the publication of this case report.

CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FIGURE LEGEND

Fig.1 (A) Endotracheal fibroscopy performed at diagnosis; (B) after one week of treatment

Fig.2 (A) CT scan at diagnosis; (B) CT scan after 8 months of treatment

REFERENCES

1 Griffin CA, Hawkins AL, Dvorak C, Henkle C, Ellingham T, Perlman EJ. Recurrent involvement of 2p23 in inflammatory myofibroblastic tumors. Cancer Res. 1999 Jun 15;59(12):2776-80. PMID: 10383129.

2 Brodlie M, Barwick SC, Wood KM, McKean MC, Welch A. Inflammatory myofibroblastic tumours of the respiratory tract: paediatric case series with varying clinical presentations. J Laryngol Otol. 2011 Aug;125(8):865-8. doi: 10.1017/S0022215111000648. Epub 2011 Apr 12. PMID: 21481297

3 Bahadori M, Liebow AA. Plasma cell granulomas of the lung. Cancer 1973;31:191–208

4 Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now? J Clin Pathol (2008) 61(4):428–37.10.1136/jcp.2007.049387

5 Höhne S, Milzsch M, Adams J, Kunze C, Finke R. Inflammatory pseudotumor (IPT) and inflammatory myofibroblastic tumor (IMT): a representative literature review occasioned by a rare IMT of the transverse colon in a 9-years-old child. Tumor (2015) 101:249–56.10.5301/tj.5000353]

6 Coffin CM, Fletcher JA. Inflammatory myofibroblastic tumor. WHO Classification of Tumours of Soft Tissue and Bone. IARC; Lyon: 2013.

7 Donner LR, Trompler RA, White RR 4th. Progression of inflammatory myofibroblastic tumor (inflammatory pseudotumor) of soft tissue into sarcoma after several recurrences. Hum Pathol. 1996 Oct;27(10):1095-8. doi: 10.1016/s0046-8177(96)90291-9. PMID: 889259

8 Morotti RA, Legman MD, Kerkar N, Pawel BR, Sanger WG, Coffin CM. Pediatric inflammatory myofibroblastic tumor with late metastasis the lung: case report and review of the literature. Pediatr Dev Pathol 2005;8:224–9

9 Dishop MK, Kuruvilla S. Primaryand metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. Arch Pathol Lab Med 2008;132: 1079–10

10 Casanova M, Brennan B, Alaggio R, Kelsey A, Orbach D, van Noesel MM, Corradini N, Minard-Colin V, Zanetti I, Bisogno G, Gallego S, Merks JHM, De Salvo GL, Ferrari A. Inflammatory myofibroblastic tumor: The experience of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG). Eur J Cancer. 2020 Mar;127:123-129.

11 Zapatero J, Lago J, Madrigal L, Baschwitz B, Perez Rodriguez E, Penalver R, Candelas J. Subglottic inflammatory pseudotumor in a 6-year-old child. Pediatr Pulmonol. 1989;6(4):268-71. doi: 10.1002/ppul.1950060411. PMID: 2748224

12 Aijaz F, Salam AU, Muzaffar S, et al: Inflammatory pseudotumor of the trachea: Report of a case in an eight-year-old child. J Laryngology Otology 108:613-616, 1994

13 Storck M, Liewald F, Heymer B, et al: Inflammatory pseudotumor of the lung and trachea. Zentralbl Chir 120:650-656, 1995

14 Dewar AL, Connet GJ: Inflammatory Pseudotumor of the Trachea in a Ten-Month-Old Infant. Pediatr Pulmonol 23:307-309, 1997

15 BumberZ, JurlinaM, Manojlovic S, Jakic -RJ. Inflammatory pseudotumor of the trachea. J Pediatr Surg 2001; 36:631 – 634.

16 Chan PW, Omar KZ, Ramanujam TM. Successful treatment of unresectable inflammatory pseudotumor of the lung with COX-2 inhibitor. *Pediatr Pulmonol* (2003) 36:167–9.10.1002/ppul.103

17 Hoseok I, Joungho H, Ahn KM, Lee SI, Jhingook K. Complete surgical resection of inflammatory myofibroblastic tumor with carinal reconstruction in a 4-year-old boy. *J Pediatr Surg* (2005) 40:e23–5.10.1016/j.jpedsurg.2005.08.043

18 Sivanandan S, Lodha R, Agarwala S, Sharma M, Kabra SK. Inflammatory myofibroblastic tumor of the trachea. *Pediatr Pulmonol* (2007) 42:847–50.10.1002/ppul.20651

19 Venizelos I, Papathomas T, Anagnostou E, Tsanakas J, Kirvassilis F, Kontzoglou G. Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature. *Pediatr Pulmonol* (2008) 43:831–5.10.1002/ppul.20869

20 Breen DP, Dubus JC, Chetaille B, Payan MJ, Dutau H. A rare cause of an endobronchial tumour in children: the role of interventional bronchoscopy in the diagnosis and treatment of tumours while preserving anatomy and lung function. *Respiration* (2008) 76:444–8.10.1159/000101718

21 Lizarbe MO, Olascoaga JH, García ER, Castiella TM, Sagaseta de Ilúrdoz Uranga María M, Garicano

JM. Paediatric myofibroblastic tumours. A presentation of three cases. *An Pediatr (Barc)* (2009) 71:331–5.10.1016/j.anpedi.2009.06.010

22 Ochs K, Hoksch B, Frey U, Schmid RA. Inflammatory myofibroblastic tumour of the lung in a five-year-old girl. *Interact Cardiovasc Thorac Surg* (2010) 10:805–6.10.1510/icvts.2009.219089

23 Sacco O, Gambini C, Gardella C, Tomà P, Rossi UG, Jassoni V, et al. "Atypical steroid response" in a pulmonary: inflammatory myofibroblastic tumor. *Pediatr Pulmonol* (2010) 45:721–6.10.1002/ppul.21237

24 Brodlie M, Barwick SC, Wood KM, McKean MC, Welch A. Inflammatory myofibroblastic tumours of the respiratory tract: paediatric case series with varying clinical presentations. J Laryngol Otol (2011) 125:865–8.10.1017/S0022215111000648

25 El-Desoky T, Nasef N, Osman E, Osman A, Zaki A, Zalata K. Endobronchial inflammatory pseudotumor: a rare cause of a pneumothorax in children. *J Bronchology Interv Pulmonol* (2013) 20:256–60.10.1097/LBR.0b013e31829bccba

26 Coffin CM, Patel A, Perkins S, Elenitoba-Johnson KS, Perlman E, Griffin CA. ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. Mod Pathol (2001) 14

27 Mossé YP, Voss SD, Lim MS, et al. Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. J Clin Oncol. 2017;35(28):3215-3221. doi:10.1200/JCO.2017.73.4830

28 Mossé YP Anaplastic Lymphoma Kinase as a Cancer Target in Pediatric Malignancies.

Clin Cancer Res. 2016 Feb 1; 22(3):546-52

29 Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, Ladanyi M, Capelletti M, Rodig SJ, Ramaiya N, Kwak EL, Clark JW, Wilner KD, Christensen JG, Jänne PA, Maki RG, Demetri GD, Shapiro GI. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med.

30 Mosse' YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study Lancet Oncol, 14 (2013), pp. 472-480

31 Sufliarsky, H.A. Gelderblom, et al. Prospective, non-randomized, multicenter, phase 2 trial of crizotinib in patients with advanced, inoperable inflammatory myofibroblastic tumor with and without anaplastic lymphoma kinase gene alterations: EORTC study 90101 CREATE Lancet Respiratory Medicine, 6 (2018), pp. 431-441).

32 Brivio E, C.M. Zwaan ALK inhibition in two emblematic cases of pediatric inflammatory myofibroblastic tumor: efficacy and side effects Pediatr Blood Cancer, 66 (5) (2019 May)

33 Craig E, Wiltsie Laura M, Lynda K. Beaupin, Ayesha Baig, Rafalkozielski David, H. Rothstein, Veetail Li, Clare J.Twistm Matthew Barth Anaplastic lymphoma kinase inhibitor therapy in the treatment of inflammatory myofibroblastic tumors in pediatric patients: Case reports and literature review, Journal of Pediatric Surgery , Feb 2021

34 Siminovich M, Galluzzo L, López J, Lubieniecki F, de Dávila MT. Inflammatory myofibroblastic tumor of the lung in children: anaplastic lymphoma kinase (ALK) expression and clinico-pathological correlation. Pediatr Dev Pathol. 2012 May-Jun;15(3):179-86. doi: 10.2350/11-10-1105-OA.1. Epub 2012 Jan 26. PMID: 22280150.)

35 Antonescu CM, Suurmeijer A. JH, Zhang L,Sung YS, Jungbluth AA, Travis WD, Al-Ahmadie H,, Fletcher C, Alaggio R.Molecular Characterization of Inflammatory Myofibroblastic Tumors with Frequent ALK and ROS1 Fusions and Rare Novel RET Gene Rearrangement. Am J Surg Pathol. 2015 Jul;39(7):957-67. doi: 10.1097/PAS.0000000000000404. PMID: 25723109; PMCID: PMC4465992.

36 Lovly CM, Gupta A, Lipson D, Otto G, Brennan T, Chung CT, Borinstein SC, Ross JS, Stephens PJ, Miller VA, Coffin CM) Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. Cancer Discov. 2014 Aug; 4(8):889-95

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