any more TNBCs harbouring NTRK gene rearrangements being identified than would have been found if testing was limited to the case classified as secretory carcinoma based on morphological findings alone.

We accept that there are some limitations to this study including its retrospective nature and, most importantly, that it was TMA based and may have missed some cases with focal expression. We also note that molecular testing was not performed on all TNBCs and the study was not designed or intended to test the sensitivity of NTRK immunohistochemistry in TNBCs.

Despite these limitations, on the basis of this study we conclude that reflex screening immunohistochemistry of all TNBCs using the rabbit monoclonal antibody EPR17341 is a valuable yield approach to identifying breast carcinomas harbouring NTRK gene rearrangements and is difficult to justify in the routine clinical setting. Given the non-specific staining demonstrated by this study, we doubt that NTRK immunohistochemistry will be useful in clinical practice to confirm a morphological suspicion of secretory carcinoma. Furthermore, if targeted therapy is being considered for a patient with a potential diagnosis of secretory carcinoma, we would recommend testing for NTRK gene rearrangements by molecular means rather than using the surrogate marker of NTRK immunohistochemistry, given its apparent lack of specificity in this setting.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

Matthew Zaborowski, Anthony J. Gill

1 Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW, Australia; 2 NSW Health Pathology, Department of Anatomical Pathology, Royal North Shore Hospital, Sydney, NSW, Australia; 3 University of Sydney, Sydney, NSW, Australia

Contact Anthony J Gill.
E-mail: affgill@med.usyd.edu.au


DOI: https://doi.org/10.1016/j.pathol.2019.04.012

Lack of clinical activity with crizotinib in a patient with FUS rearranged rhabdomyosarcoma with ALK protein overexpression

Sir,
We have previously reported on a 23-year-old male presenting with a recently described novel subtype of rhabdomyosarcoma (RMS) with a defining FUS rearrangement. This entity, first described in 2018, carries the unusual combination of myogenin, MyoD1 and ALK protein overexpression in combination with a FUS/EWSR1-TFCP2 fusion portending an aggressive clinical course. Strong cytoplasmic staining for ALK1 (ALK 01 clone) was identified on immunohistochemistry and ALK (2p23) disruption was identified in 80% of cells with loss of 5′ signal on fluorescence in situ hybridisation (FISH). Next generation sequencing confirmed a large ALK deletion of exons 2−16 (TruSight Tumour 170 panel; Illumina, USA).

Clinically, this patient had rapidly progressed through five courses of anthracycline based chemotherapy in conjunction with definitive external beam radiation to his primary sinonasal RMS. In light of the immunohistochemical (IHC) and FISH findings, and in the setting of his aggressive clinical course and chemoresistance, a decision was made with the family to self-fund crizotinib (Xalkori, PF-02341066, Pfizer) at a dose of 250 mg twice daily.

Treatment was delivered between August and September 2018. Treatment was tolerated without adverse events. Early radiological assessment was conducted after 4 weeks of therapy with evidence of stable disease in the primary sinonasal RMS but clear metabolic and morphological progression of his bilateral pleuro-pulmonary disease (Fig. 1A, B, pre crizotinib delivery; Fig. 1C, after 1 month of crizotinib). The patient was subsequently admitted for management of his symptomatic pleural effusion and unfortunately died 3 weeks later.

This case highlights the lack of clinical activity seen in the described patient in targeting ALK, which may have potential implications for other RMS patients with similar IHC, FISH and molecular correlates. The clinical activity appears contrary to other tumour subtypes where some magnitude of response in those with 5′ deletion has been reported, albeit to lesser degree than traditional 3′ and 5′ split signals. In our case, the ALK over-expression on IHC was hypothesised to represent a truncated isoform in the presence of a large ALK gene deletion without the presence of the extracellular domain. This pattern of ALK exon 2−17 deletion has been described in anaplastic large cell lymphoma and neuroblastoma leading to a truncated isoform that lacked most of the extracellular domain encompassing the LDLa domain, MAM domains, and a glycine-rich region. ALK expression by IHC using the ALK1 antibody binds within the tyrosine kinase domain at the c-terminal end of the ALK gene (exon 20−29), supporting the strong intracytoplasmic ALK protein expression observed. It is possible that ALK protein expression alone does not constitute a valid target in RMS, and that what is being demonstrated is a passenger effect, with further research required to understand the mechanisms underlying this. Alternatively, more potent signalling inhibition such as that achieved with newer generation ALK inhibitors may be required to achieve a clinically meaningful response.
Although off label targeted therapies have been explored in sarcoma, conducting prospective clinical trials assessing their efficacy in rare tumour subtypes is challenging. ALK protein expression has been documented in RMS, particularly in alveolar subtype and independent of fusion status. In embryonal subtype, the presence of ALK has been correlated with metastatic disease and poor disease specific survival. The largest study in alveolar RMS with FOX01 rearrangement showed limited clinical activity with crizotinib. In that study, many patients were unable to receive crizotinib given rapid disease progression in screening, demonstrating the aggressiveness of this entity and particularly highlighted in our case. It is unclear whether the newly described FUS-TFCP2 RMS will have the same clinical response, although our single case demonstrates that caution should be used in its delivery. Additional findings from in-house next generation sequencing (NGS) testing included a loss of function mutation in PBRM1 which has been associated with benefits from PD-1 and CTLA-4/PD-1 checkpoint blockade in renal cell carcinoma. However, given his poor performance status, no additional therapies were safely able to be delivered.

Acknowledgement: We would like to acknowledge Professor Michael Hofman for preparation of Fig. 1. Consent for publication of this case was received from the patient’s family.

Conflicts of interest and sources of funding: The NGS was available through Melbourne Genomics, funded by the State Government of Victoria (Department of Health and Human Services) and the 10 member organisations of the Melbourne Genomics Health Alliance (NHMRC Grant 113531). The authors state that there are no conflicts of interest to disclose.

Jeremy Lewin1,2,3, Jayesh Desai1,3, Kortnye Smith1, Stephen Luen1, Daniel Wong1,4,5

1Department of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Vic, Australia; 2ONTrac at Peter MacCallum Cancer Centre, Melbourne, Vic, Australia; 3Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Vic, Australia; 4Department of Anatomical Pathology, PathWest, QEII Medical Centre, Nedlands, WA, Australia; 5School of Pathology and Laboratory Medicine, The University of Western Australia, Crawley, WA, Australia

Contact Dr Jeremy Lewin.
E-mail: jeremy.lewin@petermac.org

Innocuous clinical presentation of a SMARCA4-deficient thoracic sarcoma arising in a patient with chronic empyema thoracis

Sir,

First described in 2015,1 SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS) is a recently recognised distinct tumour entity with less than 60 cases reported to date.1–5 They usually occur as large (median size ~10 cm), compressive, and locally infiltrating intra-thoracic masses in adult male smokers (median age at diagnosis 48 years, ranging from 27 to 90 years), with their epicentres located in the mediastinum or pleura/chest wall, and rarely within the lung.5 More than three-quarters of patients present with metastatic disease.5 The histopathology is of a high grade undifferentiated tumour with variably epithelioid or rhabdoid morphology and encompasses a wide range of differential diagnoses depending upon the site of origin. The tumours respond poorly to multimodality therapy, and most patients succumb to disease within 5–7 months of presentation.5 In stark contrast to the typically aggressive presentation of SMARCA4-DTS, we highlight an unusual clinical scenario wherein this tumour developed insidiously in the intercostal drain (ICD) insertion site of a patient suffering from chronic empyema thoracis.

A 60-year-old man, light smoker (~2–3 beedis/day), and a farmer by occupation, presented with sudden onset, progressively increasing breathlessness. A right ICD was placed at a private medical centre that drained ~250 mL of purulent material/day. Chest radiograph done at the time of presentation to our hospital (10 days after ICD insertion) showed presence of a multiloculated hydropneumothorax on the right side with ICD in situ (Fig. 1A).

Microbiological cultures of the pus grew more than three colonies of Gram negative bacteria, but were negative for Mycobacterium tuberculosis by GeneXpert assay. Pleural fluid cytology showed mainly polymorphs and few mesothelial cells. His serum calcium levels were within normal limits. Computed tomography (Fig. 1B–D) performed after one month showed right empyema with smooth pleural thickening and enhancement with draining catheter in situ. Lung window sections revealed bilateral apical pleural bullae and interspersed emphysematous changes in both lungs. No cavities, consolidations, mediastinal lymphadenopathy, or parenchymal mass lesions were seen. The discharge gradually reduced with time. Two months after ICD placement, there was accidental removal of the same at home and patient presented with pus discharging sinus at the ICD insertion site. A right thoracotomy was planned for thoracic window creation. Intraoperatively, loculated thick pus was seen in the posterior aspect of right pleural cavity with thickened pleura. No suspicious mass lesion was seen. Nearly 300 mL of pus was drained and an open thoracic window was created after cutting the 6th and 7th ribs just anterior to the mid-axillary line. Repeat cultures were

Fig. 1  (A) Chest radiograph 10 days after insertion of intercostal drainage tube (ICD) showed persistent multiloculated right hydropneumothorax with multiple air-fluid levels (*) and ICD in situ (arrow). (B) Axial and (C) coronal mediastinal window computed tomography sections depict right empyema with rib crowding and smooth uniformly enhancing pleural thickening. (D) Coronal lung window sections depict bilateral apical pleural bullae and interspersed emphysematous changes. (E) Follow-up chest radiographs show worsening of right effusion.