DOTATATE PET-avid Clear Cell Stromal Tumour of the Lung with *YAP1::TFE3* Fusion: Report of First Australian Case

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Abstract

Clear Cell Stromal Tumour of the Lung (CCST-L) is a recently recognised rare lung neoplasm, with only 19 cases reported in the current literature. Its histogenesis and pathogenesis remain largely unknown, however recent studies demonstrated the recurrent finding of *YAP1::TFE3* fusion, highlighting its likely contribution to the pathogenesis. Currently, the diagnosis of CCST-L is confirmed with histological findings, exclusion of lineage-specific differentiation on immunohistochemical staining and molecular testing. With previous reports of progressive disease and mortality from distant metastasis, CCST-L posts the potential of rapid progression. Currently, no general consensus has been reached for the implication of neoadjuvant or adjuvant chemotherapy in CCST-L. Its rarity also presents the difficulty in obtaining long-term follow-up and prognostication data. We herein present the first Australian case of CCST-L with *YAP1::TFE3* fusion and the first CCST-L case with DOTATATE avidity to extend our knowledge on this disease entity.

Keywords: Clear cell stromal tumour of the lung (CCST-L) • *YAP1::TFE3* fusion • DOTATATE Positron Emission Tomography (PET)

Introduction

Clear Cell Stromal Tumour of the Lung (CCST-L) was initially described in 2013 as "hemangioblastoma-like" due to its morphological comparability [1]. Since then, further cases have been reported in recent years with a total of 19 cases published in the current literature [2-7]. Recent breakthrough findings using targeted RNA-based next-generation sequencing demonstrated recurrent *YAP1::TFE3* fusions in CCST-L [5]. YAP1 is a key transcriptional coactivator downstream of the Hippo signalling pathway for the regulation of tissue homeostasis, cell cycle, and proliferation. It also exerts pro-oncogenic functions, likely providing a strong promoter for the oncogenic activation of TFE3. Previously, it has been demonstrated that the expression of *YAP1::TFE3* sufficient to cause tumour formation in *vivo* studies [8], hence further promoting its likely contribution to the pathogenesis of CCST-L. We herein present the first DOTATATE PET-avid CCST-L with YAP1::TFE3 fusion and our collaborative experience between a tertiary regional Australian healthcare centre and a quaternary metropolitan cancer centre to establish the diagnosis and further broaden the knowledge on CCST-L.

Methods

Patient consent and data collection

Informed written consent obtained directly from the patient. All information presented in this case report has been de-identified to protect patient's confidentiality. Case summary and pathological findings were obtained from electronic medical records from the hospital patient presented to. Gene fusions were detected using the TruSight RNA Fusion Panel assay (Illumina) which uses targeted RNA seq to detect fusions in 507 tumour-associated fusion genes. Fusion analysis was achieved using Arriba fusion prediction software [9].

Clinical summary

A 45-years old female, who initially presented to emergency department for investigation of left iliac fossa pain, was referred to our local oncology clinic following an incidental finding of right lower lobe pulmonary mass measuring 21 mm on CT Abdomen and Pelvis (CTAP). Further evaluation with CT chest confirmed a round solid nodule in the posterobasal Right Lower Lobe (RLL) measuring up to 22 mm (Figure 1). Subsequent DOTATATE-Positron Emission Tomography (PET) scan was suspicious for a well-differentiated Neuroendocrine Tumour (NET), without evidence of distant metastatic disease (Figure 2). The patient underwent an elective right lower lobectomy and systematic nodal dissection with a histopathological finding of a pT1c pN0 intrapulmonary neoplasm of uncertain histogenesis. Expert opinion from the quaternary cancer centre advised a clear cell stromal tumour of lung with *YAP1::TFE3* fusion identified. The case was also discussed in Lung Multidisciplinary Meeting, with post-operative surveillance recommended, and no tumour recurrence has been detected in the six months following initial diagnosis.

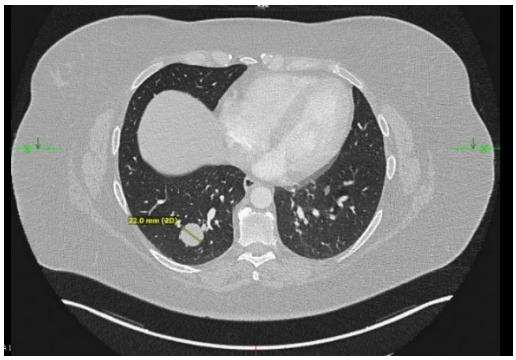

Figure 1. Computed tomography of the chest demonstrating a 22 mm round solid nodule in the posterobasal right lower lobe.

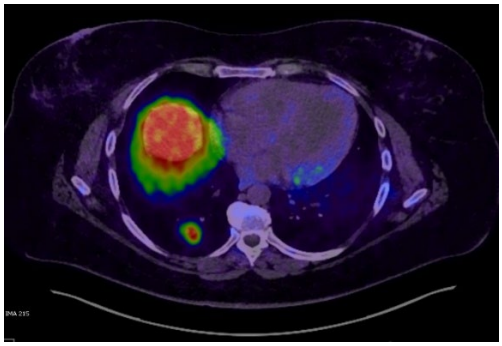

Figure 2. 68Ga-DOTA-Peptide-Positron Emission Tomography (PET) scan avidity.

Pathological findings

Grossly, there was a well circumscribed nodule in the lateral half of the inferior portion of the right lower lobe. This nodule appeared as a cystic space filled with extremely friable pale tan tissue, and measured 44 mm x 20 mm x 17 mm, SI x ML x AP (Figure 3).

Figure 3. Macroscopic appearance of the tumor, demonstrating a 44 mm × 20 mm × 17 mm well-circumscribed lesion with an apparent cystic space filled with pale tan tissue.

Microscopically, the sections showed a circumscribed tumour within lung parenchyma, composed of short spindle cells arranged in loose sheets and whorls, supported by a uniformly developed delicate fibrovascular network. The tumour nuclei displayed mild nuclear pleomorphism, with vesicular chromatin and small to medium-sized nucleoli. Occasional large atypical hyperchromatic nuclei were noted. Mitoses were infrequent. No lymphovascular invasion was identified. The lesion was clear of resection margins, and no pleural invasion was identified. Anthracotic perihilar lymph nodes examined were benign.

Immunohistochemical findings

Immunohistochemistry showed that the tumour cells showed strong reactivity for TFE3, BCL2 and vimentin, as well as weak staining with CD99. Ki-67 expression was variable, up to 10% in hot spots. Multiple cytokeratins (AE1/AE3, CAM5.2, HMWCK, CK 19, CK7, CK20, CK 5/6), EMA, CEA, Pax8, TTF1, oestrogen and progesterone receptors, GATA3, p40, SOX-10, Melan-A, HMB-45, S100 protein, synaptophysin, chromogranin, CD56, INSM1, DOG1, ERG, calcitonin, STAT6, pan-TRK, NUT, WT1, myogenin, CD21, CD35, ALK (D5F3), ROS1, desmin, smooth muscle actin and calponin were all negative. There was patchy weak staining with CD117. CD34 highlighted the vascular network, but lesional cells were negative (Figures 4-7).

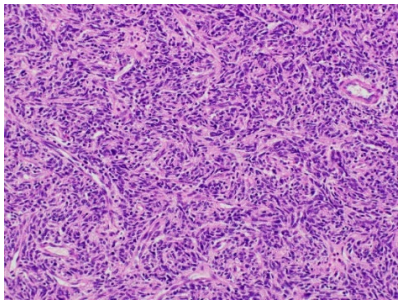

Figure 4. Photomicrograph of haematoxylin and eosin (H&E) stained section of tumour, original magnification × 200.

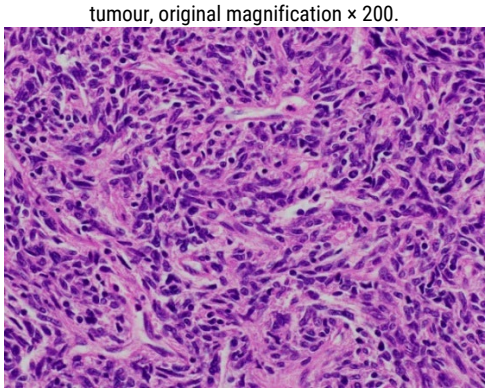

Figure 5. Photomicrograph of haematoxylin and eosin (H&E) stained section of tumour, original magnification × 200.

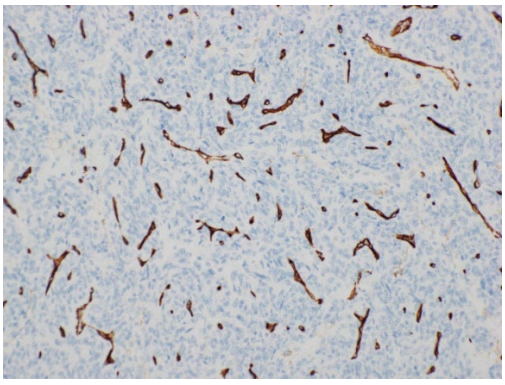

Figure 6. Immunohistochemistry for CD34 positivity showing no reactivity in tumour cells, original magnification × 200.

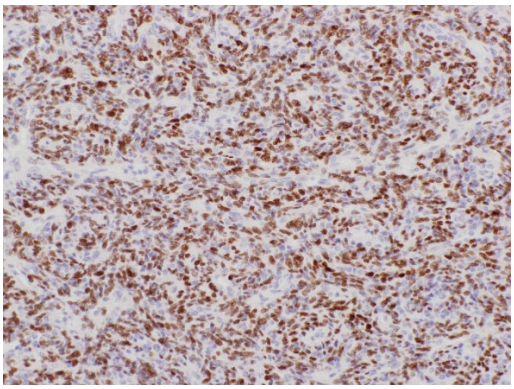

Figure 7. TFE3 is strongly and diffusely positive, original magnification × 200.

Molecular findings

A high confidence in-frame *YAP1::TFE3* fusion was detected. The resultant chimeric protein comprises an N-terminal region of YAP1, exons 1 – 4, fused to a C-terminal region of TFE3, exons 7-10, and is predicted to contain both WW domains of YAP1 and the DNA binding domain of TFE3 (Figure 8). These gene breakpoints have previously been reported in CCST-L [2-6].

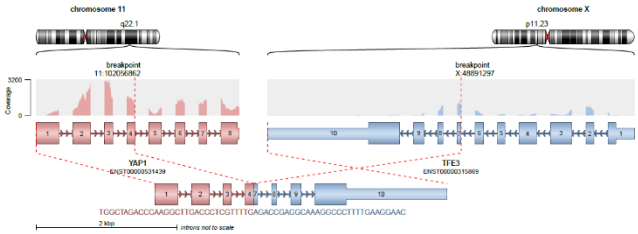

Figure 8. Targeted RNAseq fusion panel detected a *YAP1::TFE3* fusion (E).

Discussion

CCST-L posts diagnostic challenges due to its rarity and lack of lineage differentiation on IHC studies. Most of the previously reported cases were detected on CT imaging and were managed with surgical resection. Three cases reported FDG-avidity on PET scan [2,3,5]. The uniqueness of our case is its DOTATATE avidity on PET scan, which has not been previously reported in the literature. PET scan was performed as a part of the standard early lung cancer management in Australia for staging and surgical planning purposes. In addition, with the initial comment on the radiology report of a differential diagnosis of peripheral carcinoid, DOTATATE PET scan was performed. Previous studies on the diagnostic accuracy for NET have demonstrated a sensitivity of 93% and specificity of 91% of DOTATATE PET scans for the detection of primary NET [10]. Hence, it was therefore initially highly suspicious of a well-differentiated NET with its DOTATATE avidity. However, the morphology and immunophenotype were not in keeping with a NET.

Immunohistochemistry plays an important role in the diagnosis of CCST-L. Although a lack of expression of lineage-specific markers is typical (with the exception of vimentin), the expression of TFE3 may provide an important clue to the diagnosis. Furthermore, immunohistochemistry assists in excluding other differential diagnostic considerations. Hemangioblastoma has been widely considered as a differential diagnosis due to their morphological comparability, but CCST-L are usually negative for markers expressed in hemangioblastoma including S-100, CD56, NSE, alpha-inhibin, and D2-40. Additionally, hemangioblastomas are most commonly found in the central nervous system and with strong association with Von Hippel-Lindau Syndrome (VHL). There was no clinical evidence of VHL in our case, nor other cancer history or family history of VHL. Besides, there has been no single case of solitary hemangioblastoma of the lung reported so far in the current literature, and the majority of the lung hemangioblastomas are metastatic diseases, in those with a history of hemangioblastomas elsewhere in the body [7].

Another differential diagnosis of CCST-L is Perivascular Epithelioid Cell Tumour (PEComa), which also consists of epithelioid to ovoid cells with clear to granular eosinophilic cytoplasm like CCST-L, and has been reported to harbour *TFE3* gene rearrangement [11]. However, it usually expresses myomelanocytic markers such as HMB45, Melan-A, desmin and SMA, which were negative in our case. Solitary Fibrous Tumour (SFT) may show similar morphologic features, but can be excluded by negativity for CD34 and STAT6. In our case, the diagnosis of CCST-L with *YAP1::TFE3* fusion was confirmed based on histological findings, exclusion of differential diagnoses with IHC and molecular studies. With the addition of our case, this makes 11 out of the 20 cases reported positive for *YAP1::TFE3* fusion.

In light of its rare nature, CCST-L also presents management challenges to clinicians. Most of the cases reported in the current literature presented with non-specific respiratory symptoms such as chest pain, cough and dyspnoea. Similar to cases reported by Dermawan *et al.* our case was discovered incidentally and presented with non-respiratory related symptoms, and disease was found to be at early stage on histology [6]. Due to its early diagnosis, there is very limited data and no established general consensus regarding adjuvant chemotherapy. Most of the cases in literature were initially managed with surgical resection and no further intervention was required, with the exception of one unresectable case reported by Dehner *et al.* which was treated with chemotherapy [3]. In our case, the patient is under surveillance post lobectomy with routine outpatient oncology follow-up. No tumour recurrence or metastasis has been detected six months post initial resection.

Despite originally being described as benign due to its seemingly indolent nature with histological findings demonstrating low mitotic activity, two of the reported cases in the current literature showed metastatic disease, with one with distant metastasis leading to patient death 7 months post diagnosis [3,5]. Most cases reported minimal mitotic activity and necrosis on histology, however necrotic features and higher than previously reported mitotic count on histopathology, as well as bulky multifocal disease with lymph node involvement were reported in this case [3]. Therefore, this highlights the potential of rapid disease progression in CCST-L and the need for further systemic treatment research. To date, the longest follow-up duration documented in the literature is 43 months [3]. Long-term follow-up data is unavailable and is limited in most cases due to early disease courses.

Conclusion

In conclusion, we present a case of CCST-L with *YAP1::TFE3* fusion that resembles features described in previous literature. Importantly, our case demonstrated DOTATATE avidity on PET scan, which has not been reported in previous literature, further contributing to our knowledge on this disease entity. Further case reports are much needed to demonstrate the consistency of DOTATATE avidity across different cases of CCST-L to explore the potential role of DOTATATE PET scan in staging and the diagnosis of this exceedingly rare malignancy.

Data availability statement

Data sharing is not applicable to this article due to its case report nature as no datasets were generated or analysed during the case report.

Author contributions statement

SY conducted a literature review and was a major contributor in writing the manuscript. SW and NF conducted histological and immunochemical examinations of the tissue samples resected. CM, CM and DC conducted next-generation sequencing and were involved in generating the molecular results, as well as reviewing the manuscript. WF was the patient's treating oncologist and contributed to writing the manuscript. All authors read and approved the final manuscript.

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Competing interest statement

All authors declare no financial or non-financial competing interests.

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