A subset of lung adenofibromas are morphological variants of solitary fibrous tumour

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Sir: Pulmonary adenofibroma (AF) is a rare lung tumour that has been recently defined and has not yet been described in the World Health Organization classification of lung neoplasms. Breast AF and pulmonary AF show significant overlap of their morphological characteristics.[1] Recently, a subset of

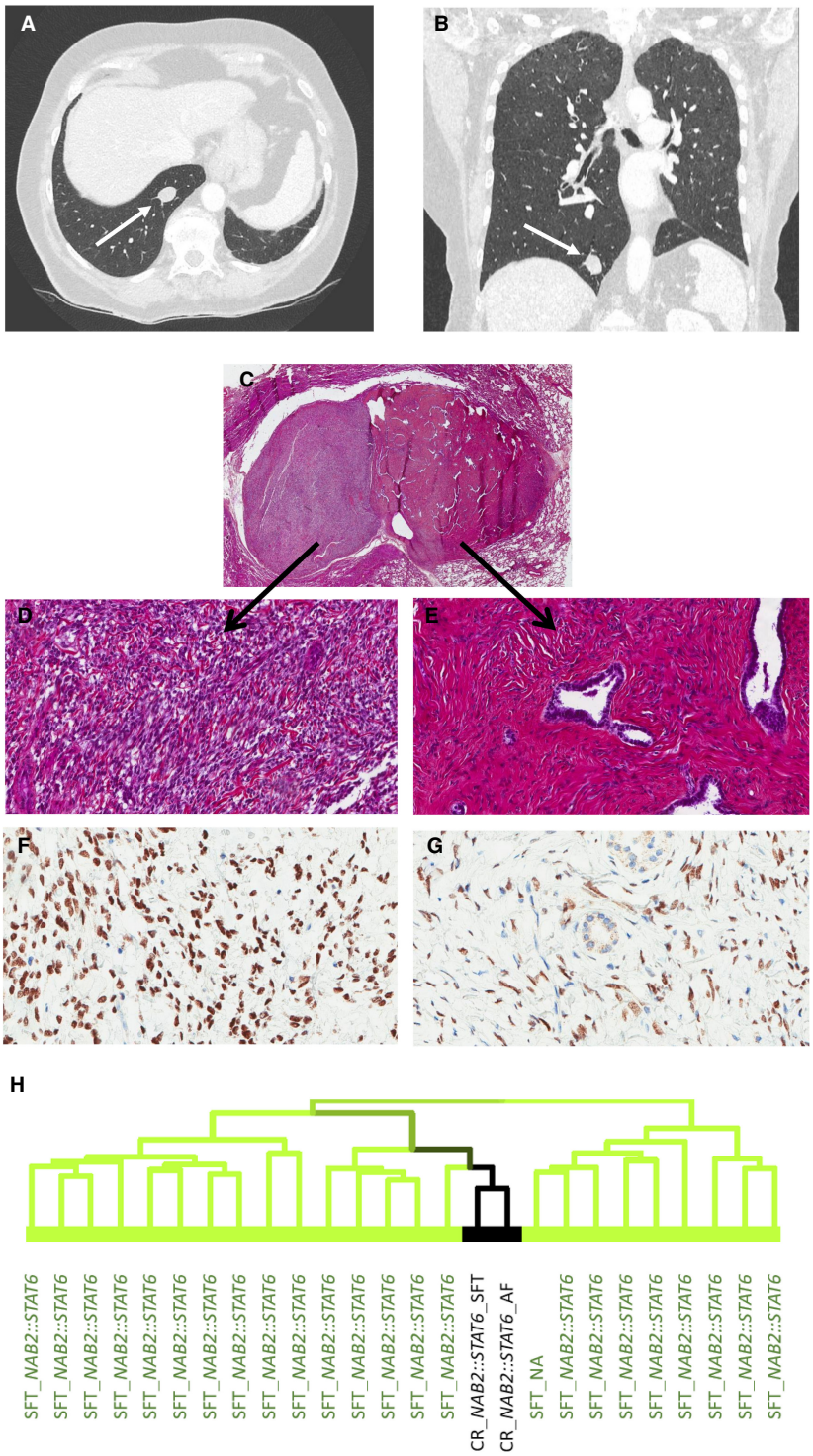


Figure 1. **A,** Computed tomography (CT) scan, axial plane, showing a right lung lower lobe tumour (arrow). **B,** CT scan, frontal plane, showing a right lung lower lobe tumour (arrow). **C,** The biphasic tumour with components of solitary fibrous tumour (SFT) (left) and adenofibroma (AF) (right) [haematoxylin and eosin (H&E)]. **D,** The SFT component with packed spindle cells (H&E). **E,** The AF component with a dense fibrous background with entrapped epithelial cells (H&E). **F,** Immunohistochemistry with anti-STAT6; nuclear staining of tumour cells in the SFT component. **G,** Immunohistochemistry with anti-STAT6; nuclear staining of tumour cells in the AF component. **H,** Excerpt from the unsupervised clustering analysis of the reference cohort expression data (Spearman correlation, 4769 samples in total), showing the inclusion of both components within the subgroup of SFTs.

pulmonary AFs have been shown to have the *NAB2*::*STAT6* fusion, the hallmark of solitary fibrous tumours (SFTs).[2] This finding raised the question of whether *STAT6*-rearranged pulmonary AF belonged to the spectrum of solitary fibrous tumours and showed lung-specific morphological features, or instead represented a distinct mesenchymal neoplasm.[3] Pleural and pulmonary SFT is a rare mesenchymal neoplasm, characterized by a monotonous proliferation of spindle cells, with variable collagenous stroma and cellularity, distinctive staghorn vasculature, strong and diffuse nuclear expression of STAT6,

Table 1. Comprehensive table of variants

						Solitary fibrous tumour		Angiofibroma	
Gene	Mutation	Exon	Type	Cosmic	ClinVar	Alteration coverage	Minor allele frequency (%)	Alteration coverage	Minor allele frequency (%)
FGFR2	c.2302_2318del: p.E768fs	18	Fsdel	NA	NA	–	–	206	70
ACVR1	c.A934G:p.I312V	8	nsSNV	NA	NA	104	46	110	53
PBRM1	c.A127G:p.T43A	2	nsSNV	NA	NA	29	52	19	33
TACC1	c.2229-1G>A	12	sp	NA	NA	6	30	17	70
ACTG1	c.803-2A>G	5	sp	NA	NA	67	73	–	–
APC	c.C6857T:p.A2286V	16	nsSNV	COSV104567088	CIOP	14	46	7	43
FGFR1	c.358+1G>C	3	sp	NA	NA	12	60	–	–

CIOP, conflicting interpretations of pathogenicity; Fsdel, frameshift deletion; NA : Not Available; nsSNV, non-synonymous SNV; sp, splicing. Genes of interest: *ACTB*, *ACTG1*, *ACVR1*, *AKT1*, *ALK*, *APC*, *ARAF*, *ARID1A*, *ARID2*, *ATM*, *ATP6AP1*, *ATP6AP2*, *ATR*, *ATRX*, *AXL*, *BAP1*, *BARD1*, *BCL2*, *BCOR*, *BCORL1*, *BIRC3*, *BRAF*, *BRCA1*, *BRCA2*, *BRIP1*, *BTK*, *CARD11*, *CCND1*, *CCND3*, *CD58*, *CD79A*, *CD79B*, *CDC42*, *CDH1*, *CDH5*, *CDH8*, *CDK12*, *CDK4*, *CDKN2A*, *CDKN2B*, *CFAP45*, *CHEK1*, *CHEK2*, *CIC*, *CIITA*, *COL2A1*, *CREBBP*, *CTNNA1*, *CTNNB1*, *CXCR4*, *CYLD*, *CYSLTR2*, *DDR2*, *DDX3X*, *DDX11*, *DDX51*, *DICER1*, *DNMT3A*, *EED*, *EGFR*, *EHD1*, *EIF1AX*, *EP300*, *ERBB2*, *ERBB4*, *ERCC2*, *ERCC5*, *ESR1*, *ETS1*, *EXT1*, *EXT2*, *EZH2*, *FANCA*, *FANCC*, *FANCD2*, *FANCL*, *FAT3*, *FBXO10*, *FBXW7*, *FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*, *FH*, *FLNA*, *FLT3*, *FLT4*, *FOXL2*, *FOXO1*, *GLMN*, *GNA11*, *GNA13*, *GNA14*, *GNAQ*, *GNAS*, *GRIN2A*, *GTF2I*, *H3F3A*, *H3F3B*, *HIST1H3B*, *HRAS*, *ID3*, *IDH1*, *IDH2*, *IL4R*, *IRF4*, *ITPKB*, *JAK1*, *KDR*, *KEAP1*, *KIT*, *KLF2*, *KMT2D*, *KRAS*, *LATS1*, *LATS2*, *LZTR1*, *MAGED1*, *MAP2K1*, *MAP2K2*, *MAP3K8*, *MAPK1*, *MDC1*, *MDM2*, *MED12*, *MEF2B*, *MEN1*, *MERTK*, *MET*, *MFHAS1*, *MITF*, *MLH1*, *MUC4*, *MRE11*, *MSH2*, *MSH6*, *MXRA5*, *MYD88*, *MYOD1*, *NBN*, *NF1*, *NF2*, *NFKBIA*, *NOD2*, *NOTCH1*, *NOTCH2*, *NRAS*, *NRG1*, *NTRK1*, *NTRK2*, *NTRK3*, *OCA2*, *PALB2*, *PBRM1*, *PDGFA*, *PDGFRA*, *PDGFRB*, *PIK3CA*, *PIK3CB*, *PIM1*, *PLCB4*, *PLCG1*, *PLCG2*, *PLEC*, *PMS2*, *POLE*, *PPARG*, *PPP2R2A*, *PPP6C*, *PRDM1*, *PREX2*, *PRKAR1A*, *PRKCA*, *PRKD1*, *PRKDC*, *PTCH1*, *PTEN*, *PTPN11*, *PTPRB*, *PTPRD*, *RAC1*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *RAF1*, *RAPGEF6*, *RARA*, *RASA2*, *RB1*, *RDX*, *RECQL4*, *RET*, *RHOA*, *ROS1*, *RYR2*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SETD2*, *SETDB1*, *SF3B1*, *SH2D2A*, *SHOC2*, *SLC45A2*, *SMAD4*, *SMARCA2*, *SMARCA4*, *SMARCB1*, *SMARCC1*, *SMO*, *SNX31*, *SOCS1*, *SOS1*,

and the *NAB2*::*STAT6* fusion. The detection of strong and diffuse nuclear expression of STAT6 by the use of immunohistochemistry has been shown to be an excellent surrogate for molecular testing.

We present a unique case showing components of both AF and SFT within the same tumour, supporting the hypothesis that pulmonary AF is a morphological variant of SFT. A round lung nodule was discovered in a 75-year-old woman with a medical history of surgically resected lung adenocarcinoma, treated with lobectomy and lymph node resection 2 years earlier. The size increase of the nodule seen on a computed tomography scan motivated surgical removal for identification. On gross examination, the nodule was well delineated from the surrounding parenchyma, white, and firm. Histological examination revealed a well-circumscribed mesenchymal neoplasm with two distinct components (Figure 1).

One-half of the tumour showed the characteristics of an SFT, and was composed of a monotonous proliferation of spindle cells with abundant collagen and staghorn vessels. Mitotic activity, pleomorphism and necrosis were absent. The second component showed the morphological features of AF, with a leaf-like growth pattern reminiscent of a phyllode tumour and cylindrical ciliated respiratory epithelium. The stroma consisted essentially of areas of acellular sclerosis. Immunohistochemistry with anti-STAT6 antibody (Abcam; Cambridge, UK YE361, 1:100) revealed diffuse nuclear expression in spindle cells of both tumour components (Figure 1), with negativity in the epithelial component.

Whole-exome RNA sequencing (TrueSeq RNA Exome; Illumina, Evry, France) on separately macrodissected components confirmed the *NAB2*::*STAT6* fusion in the AF and SFT areas.[4] AF showed a frameshift mutation of *FGFR2* (p.E768fs), which was lacking in SFT. Other mutations included non-synonymous single-nucleotide variants of *ACVR1*, *PBRM1*, and *APC*, or affected the splicing of *TACC1*, *ACTG1*, or *FGFR1* (Table 1). Unsupervised clustering of expression profiles revealed that both components matched perfectly together and within the group of SFTs[4] (Figure 1). Among cancer genes of interest, *STAT6*,

FGFR1 and *AKT2* were highly expressed in both components. In the SFT component, *ROS1*, *NKX2.1* and *GNAS* were the most highly expressed genes. *BRCA2* was underexpressed. *FOXO1* and *MAP2K4* were the most highly expressed genes in the AF component, whereas *BCORL1* was underexpressed.

Our case is unique and is the only described pulmonary biphasic tumour showing SFT and true AF components. STAT6 expression was present in both AF and SFT in our case. Although some AFs show the *NAB2*::*STAT6* fusion, the presence of this fusion does not prove that AFs are related to SFT, as some gene fusions are not specific.[2] However, the presence of two similar transcriptomic profiles is strong evidence for their close molecular relationship. Indeed, SFT can show a variety of non-classic morphological patterns, such as lipogenic and myxoid subtypes. As soft-tissue, meningeal and thoracic SFTs always lack an epithelial component, AF may represent a distinctive lung-specific growth pattern of SFT, in which the growth of the spindle mesenchymal component entraps the respiratory epithelium.[3,5] In particular, we have shown some differences in gene mutation and expression, but, because the samples were manually dissected, it is likely that the transcriptional profiles were influenced by the presence or absence of the entrapped alveolar epithelium.

The exact nature of AF has been subject to controversy and debate about its hamartomatous or neoplastic origin.[2] The nuclear expression of STAT6, the presence of the the *STAT6*::*NAB2* fusion and the possibility that a single tumour can show components of both SFT and AF are clearly not in favour of a malformative lesion, but rather indicate that *STAT6*-rearranged pulmonary AF represents a distinctive growth pattern of SFT.

The genomic alterations of *FGFR2* most frequently found in cancer include fusions, activating mutations, and amplifications.[6] To our knowledge, *FGFR2* mutations have not been described in SFTs. These alterations in *FGFR2* could be of therapeutic interest, as the fibroblast growth factor receptor inhibitor derazantinib has been shown to be beneficial in the treatment of certain tumours, such as intrahepatic cholangiocarcinomas.[6] With this unique case, which is consistent with previous data, we provide additional evidence that pulmonary AF is a subtype of SFT and should be managed as such in terms of follow-up.

Conflicts of interest

The authors declare that there are no conflicts of interest and that no funding was received for this publication.

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D. Laville wrote the draft. N. Macagno, D. Pissaloux and F. Forest critically revised the draft. A. Patoir, M. Mabrut, D. Pissaloux and M. Karanian provided clinical or pathological data or performed molecular analysis. All authors approved the final version of the manuscript.

Author Contributions

DL, NM DP and FF performed the research, DL and FF deisigned the study, MM and DP contributed essential reagents or tools, DL, NM, AP, MM, DP, MK and FF analysed the data, DL and FF wrote the paper, NM and DP critically revised the paper. All authors have read and approved the final version of the paper.

Data availability statement

Data available on request from the authors

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Accuracy of risk-stratifying gastrointestinal stromal tumours using information available during biopsy

Sir: Most gastrointestinal stromal tumours (GISTs) are localised at the time of presentation and may be found incidentally, although a percentage of GISTs are large and aggressive, capable of metastasising and causing patient death. The most common risk stratification system is probably the Armed Forces Institute of Pathology (AFIP) system, which reports risk of progression (metastasis or patient-related death) based on location, size and mitotic rate.[1] This system is endorsed by the College of American Pathologists (CAP)[2] and the Royal College of Pathologists.[3]

Fine-needle biopsy during endoscopic ultrasound is becoming more prevalent for sampling non-mucosal GI lesions, and the CAP offers a protocol for reporting GIST biopsy samples[4] as well as resection samples. However, biopsy only samples a small portion of a potentially large and heterogeneous tumour, meaning that it remains unclear whether information available at the time of biopsy (tumour size based on radiology and mitotic rate based on biopsy sample) can accurately risk-stratify GISTs.

With appropriate Institutional Research Board approval (Dana-Farber Cancer Institute Office for Human Research Studies protocol 18–473, approved 19/09/2018), we identified 66 patients from two institutions who underwent a diagnostic biopsy and subsequent surgical resection (without neoadjuvant therapy) for GIST between 2007 and 2019. We reviewed existing pathology slides on the specimens

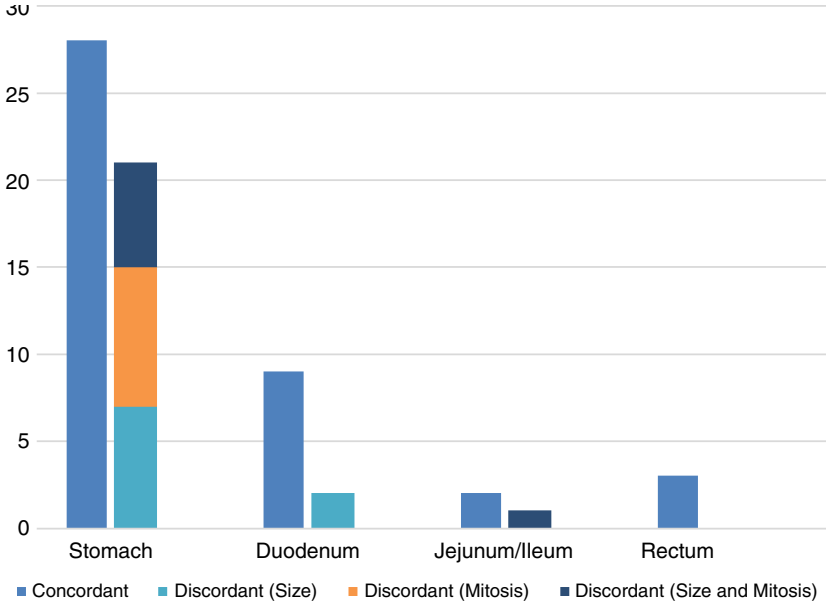


Figure 1. Concordance and discordance in risk stratification between biopsies and resections for gastric, duodenal, jejunal/ileal and rectal gastrointestinal stromal tumours (GISTs) in the cohort.