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CASE REPORTS

Identification of an Activating PDGFRA Deletion in a Novel Sinonasal Soft Tissue Neoplasm

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Abstract

Background Spindle cell tumours in the sinonasal area are diagnostically challenging. We identified a neoplasm that defied histopathological classification using current criteria.

Methods The case was subjected to histopathological, immunohistochemical and molecular analysis using a large small variant DNA panel.

Results The tumour comprised cytologically bland epithelioid spindle cells with a rich vasculature, which lack expression of actin and other smooth muscle markers, CD34 and beta-catenin. An activating insertion/deletion in exon 12 of the PDGFRA gene was detected. This alteration has previously been described in gastrointestinal stromal tumours and inflammatory fibroid polyps of the GI tract, but the site, histological, and immunophenotypic features in this tumour are distinct.

Conclusion We describe a novel sinonasal spindle cell tumour characterised by an activating insertion/deletion in exon 12 of PDGFRA. The diagnosis of PDGFRA-activated sinonasal spindle cell tumour should be considered in difficult to classify mesenchymal lesions at this site.

Keywords PDGFRA · Insertion/deletion · Sinonasal · Neoplasm

Background

The diagnosis of spindle cell tumours in the sinonasal region can be challenging, with a myriad of different entities in the histological differential diagnosis. Given these difficulties, molecular studies hold promise in accurately diagnosing and classifying this family of tumours. We describe a case of a sinonasal tumour which defied classification by routine histological assessment, in which a key molecular abnormality in PDGFRA was identified.

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Materials and Methods

Immunohistochemistry

Immunohistochemical stains using the following commercially available antibodies were performed using the Leica Bond III autostainers (Leica Biosystems): BCL2 (Dako, 1:50), CD31 (Dako, JC 70A, 1:400), CD34 (Cell Marque, QBEnd/10, 1:400), HHV8 (Abcam Anti-HHV8 antibody [LN53] 1:50), Smooth Muscle Actin (Dako, 1A4, 1:600), Desmin (Dako, D33, 1:200), Calponin (26A11, Leica, BOND™ Ready-To-Use Primary Antibody), SMMHC [BOND™ Ready-to-Use Primary Antibody Myosin Heavy Chain (smooth muscle) (S131)], DOG1 (K9) (Leica BOND™ Ready-to-Use Primary Antibody), cytokeratin MNF116 (Dako, 1:100), beta-catenin (Beta-Catenin (17C2), Leica, BOND™ Ready-to-Use Primary Antibody), STAT6 (Sigma, 1:200), S100 (Leica, BOND™ Ready-to-Use Primary Antibody), CD45 (2B11 + PD7/26, Dako, 1:50) and CD117 (CD117 (EP10) Leica, BOND™ Ready-to-Use Primary Antibody). Staining for SOX10 (SOX-10 [Cell Marque/Sigma SOX-10 (SP267)] was performed on a Ventana Benchmark IHC stainer.

DNA Extraction

Morphology of the specimen was reviewed and microdissected to approximately 40% tumour cell purity. Dissected samples were lysed in FDR Buffer with Proteinase K enzyme, and DNA extraction was performed using MagBind® TotalPure NGS kit (Omega Bio-Tek).

DNA Sequencing

Sequencing was performed using the Tru-Sight Oncology Assay (TSO500, Illumina). Briefly, DNA is quantified by Qubit testing subjected to Covaris acoustic sonication prior to sequencing library synthesis. Fragmented DNA with 5' and 3' overhangs are converted to blunt end molecules by end repair prior to the addition of an overhanging "A" tail. Sequencing adapters are ligated to the tailed fragments, followed by indexes to facilitate multiplexing of different samples. Two rounds of hybridization and capture are used to complete library preparation to give increased specificity and enrichment of target sequence.

Sequencing occurs on a NovaSeq6000 system using on board clustering and sequencing-by-synthesis technology. Library molecules bind to the flow cell and undergo bridge amplification to create clusters of identical molecules. The flowcell is then flooded with fluorescently tagged nucleotides and the complimentary nucleotide binds to the library molecule (the fluorescent label acting as a reversible terminator ensuring only one nucleotide at a time binds). The label is excited and imaged before being removed, allowing for another cycle of sequencing.

Bioinformatic Analysis

DNA is processed for variant calling of single-nucleotide variants and small deletion/insertion variants present in all exons and flanking sequence (± 20 bp) of 523 cancer-associated genes. Data were analysed with the TSO500 Local App v2.2 (Illumina) according to the user guide.

Results

Case Report

A previously well 46-year-old female presented with a history of several weeks of epistaxis and unilateral nasal blockage. Examination revealed a 5-mm mass within the nasal vestibule, arising from the septum. The lesion was biopsied and submitted for histological examination.

Histologically, the tumour was a submucosal lesion with associated pseudoepitheliomatous squamous metaplasia/hyperplasia. The tumour appeared to infiltrate and surround native glandular structures. The tumour displayed a rich vasculature, with some vessels showing haemangiopericytomatous features, others a more tortuous slit-like appearance and still others prominent mural hyalinization. A concentric perivascular growth pattern was not a feature. The tumour cells comprised a monomorphic population of plump spindle/epithelioid cells with indistinct cytoplasm and even nuclear chromatin with one to a few small nucleoli. Scattered mixed inflammatory cells are seen, but these are localised predominantly close to ulcerated areas and eosinophils were not a feature. Perivascular concentric fibrosis was not a feature (Fig. 1a, b).

Immunohistochemically, the lesional spindle cells were negative for actin (muscle specific), beta-catenin (cytoplasmic expression only), SOX10, STAT6, CD34, BCL2, HHV8, EMA, desmin, SMMHC, calponin-B, S100, cytokeratin (MNF116), DOG1, CD117, and CD45 (Fig. 1c, d).

In view of the unusual features, molecular studies were requested. An in-frame insertion/deletion in exon 12 of PDGFRA p.(S566_E571delinsR) (c.1696_1713delinsCGC) (NM_006206.6) was detected at a variant allele frequency of 21%, consistent with heterozygous mutation in the context of approximately 40% tumour cellularity (Fig. 2). Both CTNNB1 and PDGFRB were wild type, as were the other cancer-related genes tested on the panel.

MRI of the head showed no evidence of invasion of adjacent nasal structures. Neither CT of the chest, abdomen, and

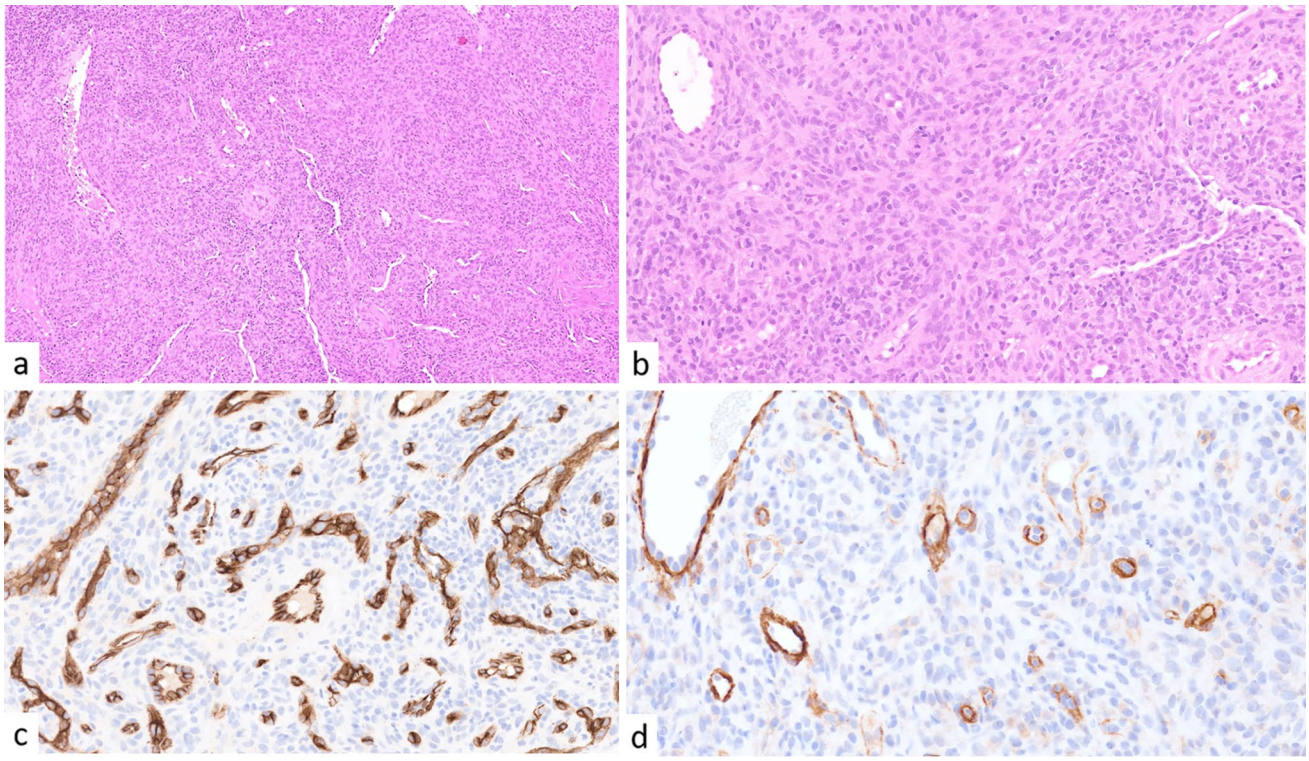

Fig. 1 **a** *H&E×50*. **b** *H&E×200* A monomorphic population of plump spindle cells set amongst a prominent vasculature with some mural hyalinisation. **c** *CD34×200*: Prominent, focally haemangiopericytomatous vasculature. **d** *Smooth muscle actin×200:* Absence of myoid differentiation immunophenotypically

pelvis nor gastric endoscopy showed evidence of distant tumour. A wider excision of the nasal lesion showed no evidence of residual tumour. As of 1-year post-excision, there is no evidence of recurrence or metastatic disease.

Conclusion

We describe, to our knowledge for the first time, a histologically distinctive sinonasal spindle cell tumour characterised by an in-frame insertion/deletion of PDGFRA.

PDGFRA is a receptor tyrosine kinase, with an extracellular immunoglobulin-like domain and an intracellular kinase domain that is widely implicated in human neoplasia [1]. The gene shows a range of activating alterations across several tumour types. Most commonly, single-nucleotide variant mutations target the intracellular kinase domain (with hotspots in exons 14 and 18), with a smaller number targeting the extracellular domain. A further hotspot for alterations is disruption of the autoinhibitory juxtamembrane domain (exon 12), as is seen in the current case, and the precise S566_E571delinsR identified has been shown to lead to constitutive activation of PDGFRA in vitro [2].

Specifically within the spectrum of mesenchymal tumours, mutations in PDGFRA are particularly characteristic of two soft tissue neoplasms, and interestingly, the genetic alterations previously described in these two tumours target the same region of the gene that is altered in our case. The first is the intestinal inflammatory fibroid polyp (IFP). This is a benign neoplasm which can occur throughout the gastrointestinal (GI) tract. This tumour shows distinctive histology, with a hypocellular appearance, with short spindled to stellate cells in an oedematous or myxoid stroma, often with an accompanying inflammatory infiltrate of eosinophils and lymphocytes and occasional perivascular concentric 'onion skin' fibrosis. CD34 immunostaining is typically positive. This lesion is characterised by alterations in PDGFRA, but the precise alteration varies by localisation in the GI tract with gastric tumours preferentially showing alterations in exon 18, and small intestinal tumours showing alterations in exon 12, most commonly the S566_E571delinsR variant identified in our current sinonasal case [3, 4]. The second neoplasm in which this particular PDGFRA alteration has been recurrently identified is gastrointestinal stromal tumour (GIST). The alteration most commonly seen in PDGFRA mutant GIST targets the kinase domain in exon 18, but a smaller number of cases have been described as carrying the S566_E571delinsR (or K) variant [2, 5]. In contrast to IFP, PDGFRA exon 12-altered GIST are much

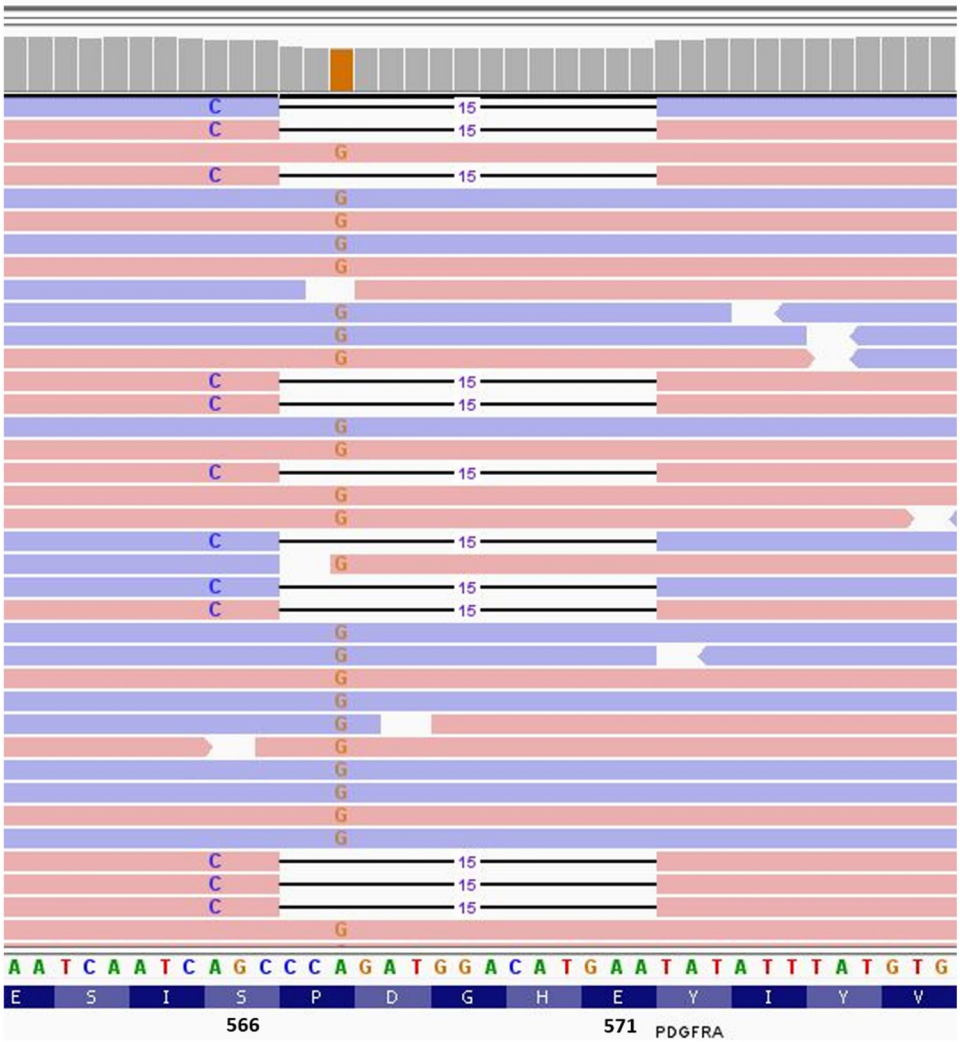

Fig. 2 The exon 12 PDGFRA S566_E571delinsR alteration identified in the tumour (via Integrated Genome Viewer) (NB: A known synonymous SNP in codon 567 is present in the wild-type allele)

more commonly seen in the stomach. The typical histology in PDGFRA mutant GIST is of striking epithelioid cell change, and DOG1 is invariably positive. The histology and immunophenotype in the current case differs from that seen in both of these entities, suggesting it is a novel neoplasm rather than a rare example of either of these entities occurring at a sinonasal site.

Whilst our case shows some histological similarity to a myofibroma/myopericytoma, actin staining is negative, and no alteration in the key PDGFRB driver was identified. Similarly, a sinonasal glomangiopericytoma is within the differential diagnosis, but CD34 is negative and there is no evidence of a CTNNB1 mutation or nuclear beta-catenin immunoreactivity. Solitary fibrous tumours can show similar vascular patterning and cytology but are typically CD34 and STAT6 positive. However, given the large range and histological diversity of soft tissue lesions arising at this site, we suggest testing for this abnormality in the case of any difficult to classify nasal spindle cell neoplasm.

Here we report an example of a novel nasal spindle cell tumour in which an activating PDGFRA exon 12 indel was detected as the sole driver. Based on the histological features, the clinical course of this case and the largely indolent course pursued by other mesenchymal tumours characterised by this genetic variant, the lesion is likely to pursue a benign course, but rare cases of metastatic disease have been described in PDGFRA-altered GIST. The fact that this PDGFRA alteration is an activating mutation conferring sensitivity to imatinib means that use of this drug could be considered should a case arise in which resection is not feasible. Following its recognition, clinical studies of a larger series of cases of this entity is warranted to ascertain more completely its clinical behaviour and pathological spectrum.

Author Contributions All authors contributed to the study conception and design. Collection of clinical data was performed by HH, FA and SM. Data acquisition and analysis were performed by JW, JT, JB and PT. The first draft of the manuscript was written by JW and all authors

commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability The genomic data for this case have been submitted to the Catalogue Of Somatic Mutations In Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cosmic). The data have been assigned the signifier COSP51117 and will be made public following the variant being associated with a PubMed ID.

Code Availability Analysis was performed using commercially available proprietary software TSO500 Local App v2.2 (Illumina).

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

Ethical Approval Local ethical approval was waived in view of the retrospective nature of the study and all the procedures performed being part of the routine care.

Research Involving Humans and/or Animals This article does not contain any experimental studies with human or animal subjects.

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