Pathology - Research and Practice 232 (2022) 153803

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Short communication

A mesenchymal chondrosarcoma with aberrant nuclear expression of STAT6: a potential diagnostic pitfall

Giuseppe Broggi [a], Manuel Mazzucchelli [a], Renato Covello [b], Beatrice Casini [b], Giuseppe Maria Vincenzo Barbagallo [c,d], Lucia Salvatorelli [a], Gaetano Magro [a,*]

[a] Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Anatomic Pathology, University of Catania, 95123 Catania, Italy
[b] Pathology Department, Regina Elena National Cancer Institute IRCCS, 00168 Rome, Italy
[c] Department of Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Neurological Surgery, Policlinico "Rodolico-San Marco" University Hospital, University of Catania, 95123 Catania, Italy
[d] Interdisciplinary Research Centre on the Diagnosis and Therapy of Brain Tumors, University of Catania, 95123 Catania, Italy

ARTICLE INFO

Keywords:
Mesenchymal chondrosarcoma
STAT6
HEY1-NCOA2 fusion gene
NAB2-STAT6 fusion gene
Diagnostic pitfall

ABSTRACT

STAT6 is usually considered to be a very sensitive and specific immunomarker for diagnosis of solitary fibrous tumor (SFT), being a surrogate of the *NAB2-STAT6* fusion gene identified in most cases of this tumor. STAT6 expression has also been reported in rare cases of other soft tissue tumors, such as low-grade fibromyxoid sarcoma, myxoid/round cell liposarcoma, dedifferentiated liposarcoma and deep fibrous histiocytoma. The aim of this study was to report, for the first time, a case of mesenchymal chondrosarcoma showing diffuse aberrant immunohistochemical expression of STAT6. Molecular biology, showing the *HEY1-NCOA2* fusion gene, was crucial to rule out SFT.

1. Introduction

Diffuse nuclear staining for STAT6 is very sensitive and specific to solitary fibrous tumor (SFT), since it was first reported in 2013 as an immunohistochemical surrogate of the *NAB2-STAT6* fusion gene [1–6].

In the last years, different studies have also described STAT6-immunoreactivity in a small group of other mesenchymal tumors, including low-grade fibromyxoid sarcoma, myxoid/round cell liposarcoma, dedifferentiated liposarcoma, deep fibrous histiocytoma, ovarian fibroma and pulmonary adenofibroma [4,7,8].

To the best of our knowledge, we herein report the first case of mesenchymal chondrosarcoma (MC) with a diffuse aberrant nuclear expression of STAT6, which can represent a potential diagnostic pitfall.

MC is a high-grade, round cell malignant mesenchymal tumor that accounts for 2–4% of all chondrosarcomas [9]. It may have a widespread anatomical distribution, including bones (mainly the jaw, ribs, ilium, vertebrae and lower extremities), soft tissues and intracranial sites. Most MCs (>90%) harbor a highly specific gene fusion, originating from a chromosomal deletion between exon4 of *HEY1* and exon13 of *NCOA2* (*HEY1-NCOA2*) [10]. Histologically, MC exhibits a biphasic morphology, being composed of small to medium-sized, poorly differentiated round cells with scant cytoplasm and a peculiar staghorn/hemangiopericytoma-like vascular pattern, variably mixed with islands of well-differentiated hyaline cartilage. Immunohistochemistry usually shows variable positivity for CD99, S-100 protein and SOX9, while the nuclear expression of SMARCB1 (INI-1) is typically retained. There may be an aberrant expression of EMA, desmin, myogenin and MYOD1. Interestingly NKX3.1 and OLIG-2 have been reported as immunohistochemical surrogates of the *HEY1-NCOA2* gene fusion [11–13].

We herein present a unique case of MC with aberrant nuclear expression of STAT6 in a 67-year-old woman, emphasizing the differential diagnostic problems with SFT. Molecular analyses were crucial for the correct diagnosis.

2. Materials and methods

A 67-year-old woman, diagnosed one month before for a breast invasive carcinoma of no special type (grade 1; luminal A), was admitted to the Neurosurgery Unit of our hospital for the acute onset of back pain; she underwent a spine MRI which showed a solid, bone destructive lesion of 82 × 60 × 73 mm, which deformed and swelled the posterior

* Corresponding author.
E-mail address: g.magro@unict.it (G. Magro).

https://doi.org/10.1016/j.prp.2022.153803
Received 5 December 2021; Received in revised form 4 February 2022; Accepted 9 February 2022
Available online 11 February 2022

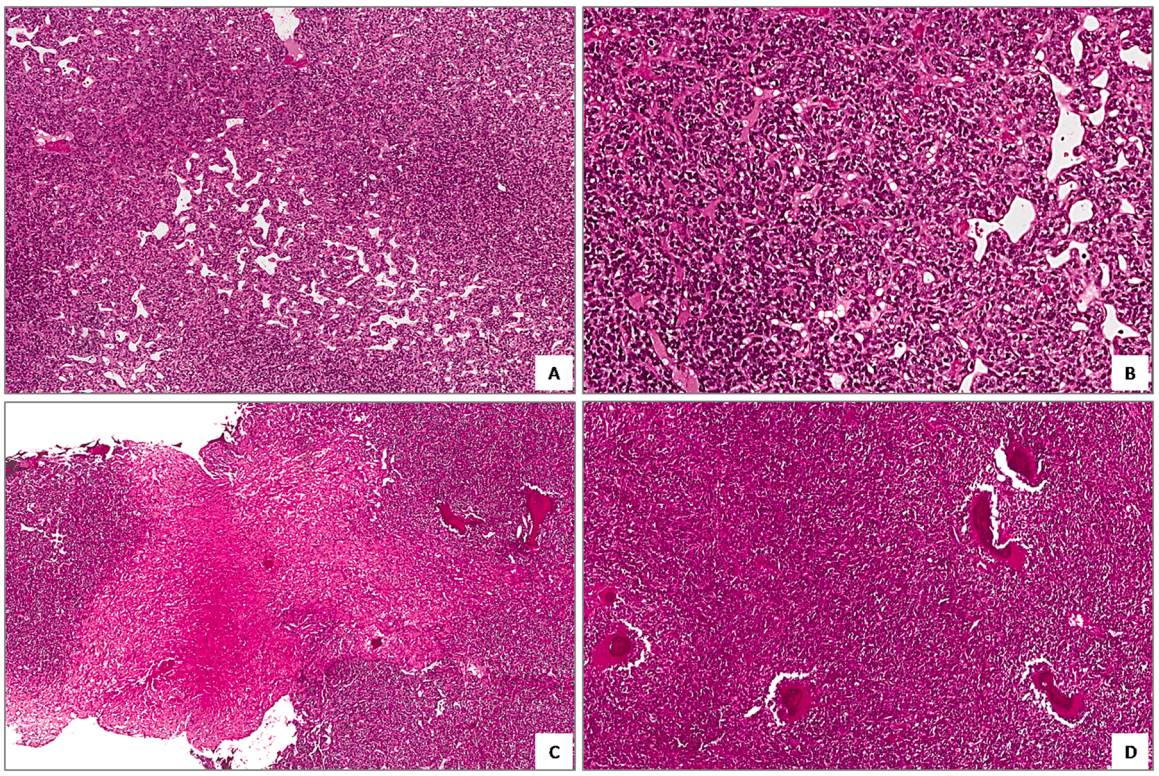

Fig. 1. Morphology. (A) Low magnification showing a hypercellular tumor composed of small to medium-sized round cells with a hemangiopericytomatous vascular pattern (H&E; original magnification 100x). (B) On higher magnification, round cells with hyperchromatic nuclei and scant cytoplasm are seen (H&E; original magnification 200x). (C) Tumor focally exhibits alternating hypercellular and hypocellular fibrotic areas (H&E; original magnification 50x). (D) A diffuse infiltration of mature bone tissue is shown (H&E; original magnification 100x).

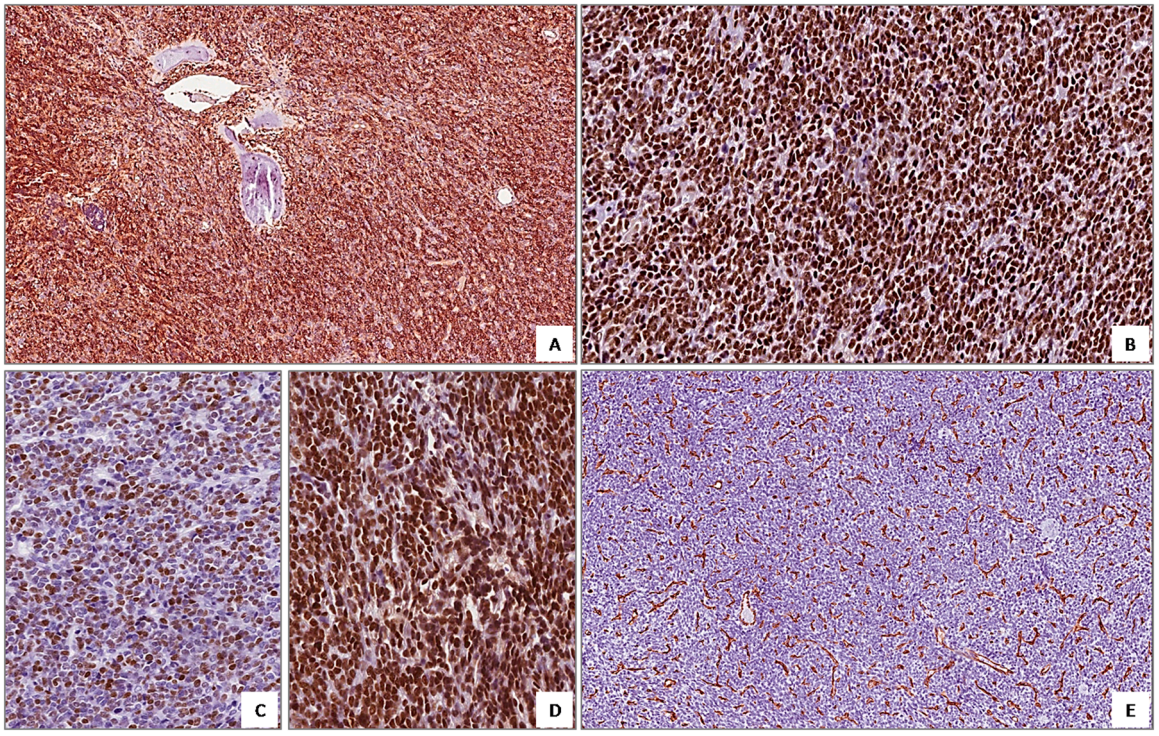

Fig. 2. Immunohistochemistry. Neoplastic cells are strongly and diffusely stained with CD99 (A), STAT6 (B), OLIG-2 (C) and NKX3.1 (D) (immunoperoxidase; original magnifications 100× (A), 300× (B-D). (E) Neoplastic cells are completely negative for CD34 (immunoperoxidase; original magnification 100×).

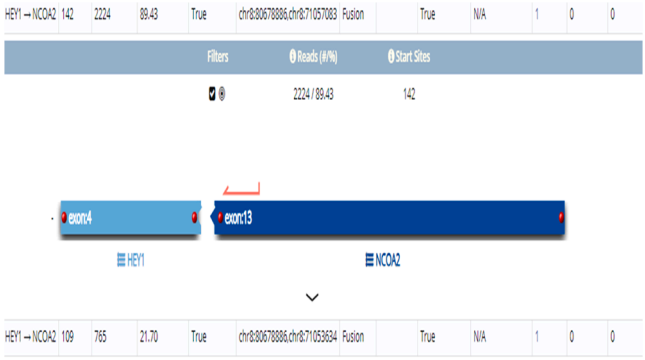

Fig. 3. Molecular analysis. Schematic representation of the presence of the chimeric transcript between exon4 of *HEY1* and exon13 of *NCOA2*, identified by Next Generation sequencing.

walls of the soma of Th2 and Th3 vertebrae, likely metastatic in nature. Accordingly, the patient underwent neurosurgery to stabilize the fracture and remove the pathologic tissue. Surgical sample was formalin-fixed, paraffin-embedded, cut to 5 μm and stained with hematoxylin and eosin (H&E). Immunohistochemical analyses were performed and the following antibodies were tested: STAT6, CD99, INI-1, SAT-B2, CD34, S-100, pancytokeratins, TTF-1, EMA, chromogranin A, synaptophysin, desmin, myogenin, OLIG-2 and NKX3.1. Molecular biology analyses through Next Generation-sequencing (NGS) were performed to search for *NAB2-STAT6* and *HEY1-NCOA2* fusion genes.

3. Results

The histological examination showed a hypercellular, mesenchymal neoplasm, exclusively composed of small to medium-sized, round to ovoidal-shaped, poorly differentiated cells with hyperchromatic nuclei and scant cytoplasm (Fig. 1a), and a diffuse thin-walled vascular component, frequently arranged in a staghorn/hemangiopericytoma-like growth pattern (Fig. 1b). Focal alternating hypocellular and hypercellular areas were observed (Fig. 1c). The tumor diffusely infiltrated fragments of mature bone tissue (Fig. 1d). Mitoses (5 mitoses/10 HPF) and rare foci of necrosis (<10%) were seen. Neither atypical mitoses nor islands of cartilage were found. Based on the morphology alone, the main differential diagnoses included SFT, MC, Ewing's sarcoma and Ewing's-like sarcomas.

Immunohistochemically, neoplastic cells were strongly and diffusely stained with CD99 (Fig. 2a), STAT6 (Fig. 2b), SAT-B2, OLIG-2 (Fig. 2c) and NKX3.1 (Fig. 2d). Nuclear expression of INI-1 was retained while CD34 (Fig. 2e), S100, epithelial and myogenic markers were all negative. The diffuse nuclear expression of STAT6 was an unexpected finding and favored the diagnosis of SFT. Conversely, the diffuse immunostaining for CD99, OLIG-2 and NKX3.1 was more consistent with a MC. Given the ambiguous morphological and immunohistochemical profile of the tumor, we performed molecular analyses to confirm the presence of *NAB2-STAT6* fusion gene. NGS analysis showed the absence of *NAB2-STAT6* fusion, but revealed the presence of the *HEY1* (exon4)-*NCOA2* (exon13) chimeric transcript (Fig. 3). Based on a combined evaluation of morphological, immunohistochemical and molecular features, the diagnosis of "*mesenchymal chondrosarcoma with aberrant nuclear expression of STAT6*" was rendered.

The patient underwent oncological medical treatment and she is currently asymptomatic but with local residual of disease, as evidenced at PET/TC imaging after 6 months of follow-up.

4. Discussion

In recent years, numerous studies have proved that the diffuse nuclear immunohistochemical expression of STAT6 is very sensitive and specific to SFT, being a prompt surrogate of *NAB2-STAT6* fusion transcript [1–6]. A nuclear positivity for STAT6 has also been occasionally described in soft tissue tumors, such as a low-grade fibromyxoid sarcoma, myxoid/round cell liposarcoma, dedifferentiated liposarcoma and deep fibrous histiocytoma [4,7]. All the cases of MCs previously tested for STAT6 have been found to be STAT6-negative [4,13]. The aim of the present study is to emphasize the possibility of a diffuse aberrant nuclear expression of STAT6 in MC, suggesting the diagnostic utility of molecular analyses in soft tissue tumors with ambiguous immunohistochemical profile. MC may be difficult to be distinguished from Ewing's sarcoma/Ewing's sarcoma-like tumors or from SFT based on morphology alone, especially when dealing with small biopsies in which, as in the present case, a small cell component is present solely along with the lack of a cartilaginous component. The polyphenotypic profile of the tumor (positivity for CD99, SAT-B2, STAT6, OLIG2 and NKX3.1) suggested to us to perform molecular biology analyses. The presence of *HEY1-NCOA2* fusion gene combined with the diffuse immunohistochemical expression of OLIG-2 and NKX3.1 (considered as surrogates of this fusion gene), along with the absence of *NAB2-STAT6* chimeric transcript, was consistent with the diagnosis of MC.

5. Conclusions

In conclusion, we emphasize that the aberrant nuclear expression of STAT6 in MC may represent a diagnostic pitfall and that pathologists should be aware of this possibility to avoid diagnostic errors. However, further studies on a larger series of MCs are required to establish the exact percentage of STAT6-positive MCs.

6. Compliance with ethical standards

The study complied with the Ethical Principles for Medical Research Involving Human Subjects according to the World Medical Association Declaration of Helsinki; the non-interventional, retrospective nature of our study did not require any informed consent, even if a written informed consent had been obtained from the patient before surgical procedures. The clinical information had been retrieved from the patients' medical records and pathology reports. Patients' initials or other personal identifiers did not appear in any image. Finally, all samples were anonymized before histology, immunohistochemistry and molecular analysis; therefore, no further ethical approval was necessary to perform the study.

Funding

This research received no external funding.

CRediT authorship contribution statement

Giuseppe Broggi: Conceptualization, Investigation, Writing - original draft. **Manuel Mazzucchelli:** Methodology, Writing – original draft. **Renato Covello:** Methodology, Resources. **Beatrice Casini:** Formal analysis, Resources. **Giuseppe Maria Vincenzo Barbagallo**: Resources. **Lucia Salvatorelli:** Formal analysis, Data curation. **Gaetano Magro:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data are available from the corresponding author upon reasonable request.

References

[1] L. Schweizer, C. Koelsche, F. Sahm, R.M. Piro, D. Capper, D.E. Reuss, S. Pusch, A. Habel, J. Meyer, T. Göck, D.T. Jones, C. Mawrin, J. Schittenhelm, A. Becker, S. Heim, M. Simon, C. Herold-Mende, G. Mechtersheimer, W. Paulus, R. König, O. D. Wiestler, S.M. Pfister, A. von Deimling, Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein, Acta Neuropathol. 125 (2013) 651–658, https://doi.org/10.1007/s00401-013-1117-6.

[2] A.L. Cheah, S.D. Billings, J.R. Goldblum, P. Carver, M.Z. Tanas, B.P. Rubin, STAT6 rabbit monoclonal antibody is a robust diagnostic tool for the distinction of solitary fibrous tumour from its mimics, Pathology 46 (2014) 389–395, https://doi.org/10.1097/PAT.0000000000000122.

[3] C. Koelsche, L. Schweizer, M. Renner, A. Warth, D.T. Jones, F. Sahm, D.E. Reuss, D. Capper, T. Knösel, B. Schulz, I. Petersen, A. Ulrich, E.K. Renker, B. Lehner, S. M. Pfister, P. Schirmacher, A. von Deimling, G. Mechtersheimer, Nuclear relocation of STAT6 reliably predicts NAB2-STAT6 fusion for the diagnosis of solitary fibrous tumour, Histopathology 65 (2014) 613–622, https://doi.org/10.1111/his.12431.

[4] A. Yoshida, K. Tsuta, M. Ohno, M. Yoshida, Y. Narita, A. Kawai, H. Asamura, R. Kushima, STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors, Am. J. Surg. Pathol. 38 (2014) 552–559, https://doi.org/10.1097/PAS.0000000000000137.

[5] G. Magro, L. Salvatorelli, E. Piombino, G.M. Vecchio, G. Broggi, S. Castorina, Solitary fibrous tumor with atypical features of the paravesical space: benign clinical course at the 10-years follow-up. Report of a case and review of the literature, Pathologica 112 (2020) 200–209, https://doi.org/10.32074/1591-951X-126.

[6] G. Magro, G. Angelico, A. Righi, S. Benini, L. Salvatorelli, J. Palazzo, Utility of STAT6 and 13q14 deletion in the classification of the benign spindle cell stromal tumors of the breast, Hum. Pathol. 81 (2018) 55–64, https://doi.org/10.1016/j.humpath.2018.06.015.

[7] L.A. Doyle, M. Vivero, C.D. Fletcher, F. Mertens, J.L. Hornick, Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics, Mod. Pathol. 27 (2014) 390–395, https://doi.org/10.1038/modpathol.2013.164.

[8] N. Fusco, E. Guerini-Rocco, C. Augello, A. Terrasi, G. Ercoli, C. Fumagalli, D. Vacirca, P. Braidotti, A. Parafioriti, M. Jaconi, L. Runza, V. Ananthanarayanan, F. Pagni, S. Bosari, M. Barberis, S. Ferrero, Recurrent NAB2-STAT6 gene fusions and oestrogen receptor-α expression in pulmonary adenofibromas, Histopathology 70 (2017) 906–917, https://doi.org/10.1111/his.13165.

[9] J.H. Choi, J.Y. Ro, The 2020 WHO classification of tumors of bone: an updated review, Adv. Anat. Pathol. 28 (2021) 119–138, https://doi.org/10.1097/PAP.0000000000000293.

[10] L. Wang, T. Motoi, R. Khanin, A. Olshen, F. Mertens, J. Bridge, P. Dal Cin, C. R. Antonescu, S. Singer, M. Hameed, J.V. Bovee, P.C. Hogendoorn, N. Socci, M. Ladanyi, Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data, Genes Chromosomes Cancer 51 (2012) 127–139, https://doi.org/10.1002/gcc.20937.

[11] K. Yao, Z. Duan, S. Yang, Z. Du, Y. Wang, X. Qi, OLIG2 immunolabeling of mesenchymal chondrosarcoma: report of 14 cases, J. Neuropathol. Exp. Neurol. 79 (2020) 959–965, https://doi.org/10.1093/jnen/nlaa079.

[12] M. Syed, S. Mushtaq, A. Loya, U. Hassan, NKX3.1 a useful marker for mesenchymal chondrosarcoma: an immunohistochemical study, Ann. Diagn. Pathol. 50 (2021), 151660, https://doi.org/10.1016/j.anndiagpath.2020.151660.

[13] N. Ramanayake, A.C. Vargas, J. Talbot, F. Bonar, D.D. Wong, D. Wong, A. Mahar, R. Karim, P.P. Luk, C. Selinger, L. Sioson, A.J. Gill, F. Maclean, NKX3.1 immunohistochemistry is highly specific for the diagnosis of mesenchymal chondrosarcomas: experience in the Australian population, Pathology 53 (2021) 705–712, https://doi.org/10.1016/j.pathol.2020.11.007.