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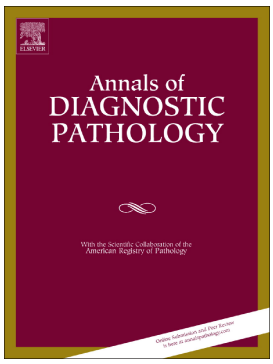

COL1A1 is a fusionpartner of USP6 in myositis ossificans – FISH analysis of six cases

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Letter to the Editor

COL1A1 is a fusionpartner of _USP6_ in myositis ossificans – FISH analysis of six cases

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Dear Editor,

USP6 rearrangement is a consistent genetic driver event in nodular fasciitis, aneurysmal bone cyst and giant cell lesion of small bones. These lesions belong to the group of self-limiting diseases of soft tissue and bone showing histologically a cell culture-like myofibroblastic proliferation merging variably with osteoid and bone and osteoclastic giant cells [1,2]. Recently, we identified *USP6* rearrangements in myositis ossificans expanding the spectrum of the mentioned clonal transient neoplasms [3].

Sukov et al investigated twelve cases of myositis ossificans and found in two instances *USP6* rearrangements. They referred them to as aneurysmal bone cyst of soft tissue and demonstrated *USP6-COL1A1* in one case [4]. Another case of soft tissue aneurysmal bone cyst showed cytogenetically a translocation t(17;17)(p13;q21) corresponding to *COL1A1* and *USP6* loci [5].

This prompted us to analyze *COL1A1* FISH in our reported *USP6* rearranged myositis ossificans cases by Bekers et al [3].

USP6 signals were considered positive if at least 20% of the 50 counted cells showed split signals.

Four out of six cases harbored *COL1A1* rearrangement (Figure 1) indicating *COL1A1-USP6* fusions in a subset of myositis ossificans.

It seems that the *COL1A1* promotor binds to the *USP6* coding sequence leading to transcriptional upregulation and oncogenic activation of USP6. This mechanism is similar to the remaining *USP6*-related fusion genes in all other lesions mentioned above [1]. *COL1A1-USP6* has also been identified in aneurysmal bone cyst underpinning a relationship. It is therefore not surprising that overlapping features of myositis ossificans and aneurysmal bone cyst of soft tissue are discussed [6].

References

[1] Oliveira AM, Chou MM. USP6-induced neoplasms: the biologic spectrum of aneurysmal bone cyst and nodular fasciitis. Hum Pathol 2014;45:1-11.

[2] Agaram NP, LeLoarer FV, Zhang L, Hwang S, Athanasian EA, Hameed M, Antonescu CR. *USP6* gene rearrangements occur preferentially in giant cell reparative granulomas of the hands and feet but not in gnathic location. Hum Pathol 2014;45:1147-1152.

[3] Bekers EM, Eijkelenboom A, Grünberg K, Roverts R, de Rooy JW, van der Geest IC, van Gorp JM, Creytens D, Flucke U. Myositis ossificans – another condition with USP6 rearrangement, providing evidence of a relationship with nodular fasciitis and aneurysmal bone cyst. Ann Diagn Pathol 2018;34:56-59

[4] Sukov WR, Franco MF, Erickson-Johnson M, Chou MM, Unni KK, Wenger DE, Wang X, Oliveira AM. Frequency of *USP6* rearrangements in myositis ossificans, brown tumor, and cherubism: molecular cytogenetic evidence that a subset of "myositis ossificans-like lesions" are the early phases in the formation of soft-tissue aneurysmal bone cyst. Skeletal Radiol 2008;37:321-327.

[5] Jacquot C, Szymanska J, Nemana LJ, Steinbach L, Horvai A. Soft-tissue aneurysmal bone cyst with translocation t(17;17)(p13;q21) corresponding to COL1A1 and USP6 loci. Skeletal Radiol 2015;44:1695-1699.

[6] Nielsen GP, Fletcher CD, Smith MA, Rybak L, Rosenberg AE. Soft tissue aneurysmal bone cyst: a clinicopathological study of five cases. Am J Surg Pathol 2002;26:64-69.

Figure legend

COL1A1 FISH shows break apart signals indicating rearrangement.

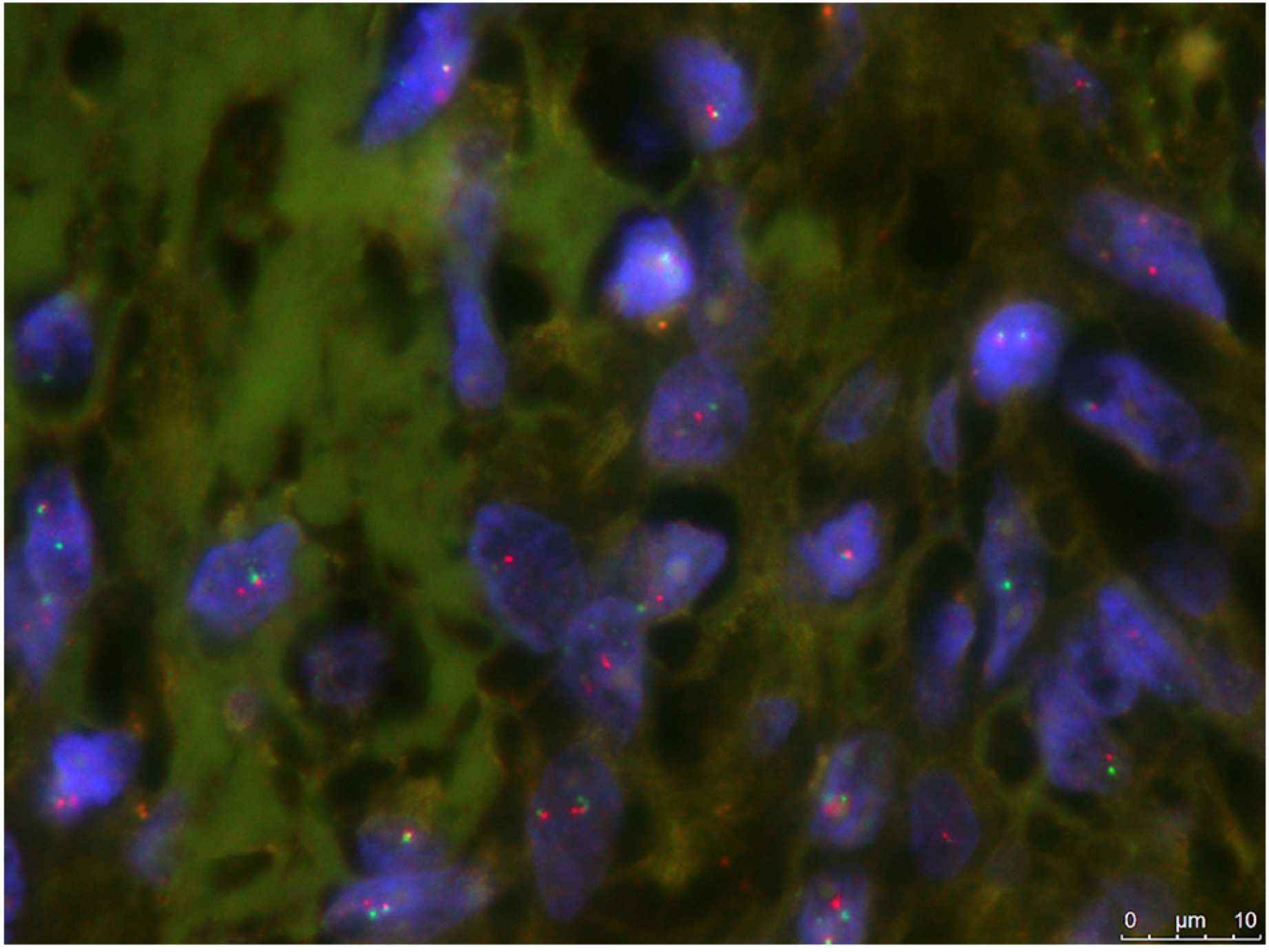

Figure 1