P309. Cutaneous angiosarcomas: molecular landscape beyond MYC deregulation

Andrea Ronchi[a*], Federica Zito Marino[b], Stefano Lucà[b], Giovanni Savarese[c], Giuseppe Argenziano[d], Elvira Moscarella[d], Antonio Cossu[e], Giuseppe Palmieri[f], Annarosaria De Chiara[g], Renato Franco[b]

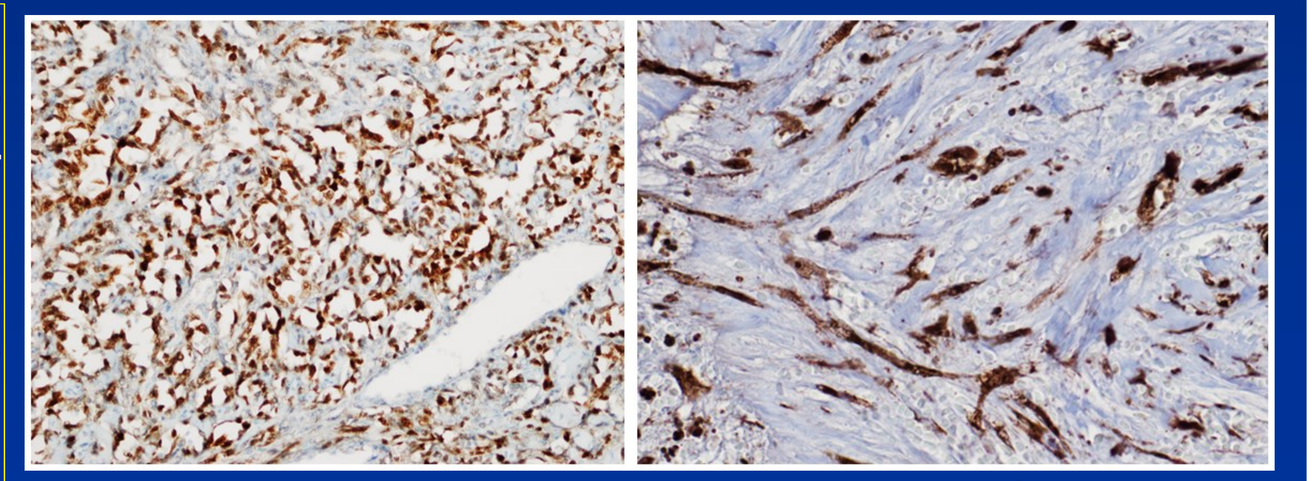
*a: Pathology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy. E-mail address: andrea.ronchi@unicampania.it. b: Pathology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy. c: AMES-Centro Polidiagnostico Strumentale srl, 80013 Naples, Italy. d: Dermatology Unit, Department of Mental and Physical Health and Preventive Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy. e: Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100, Sassari, Italy. f: Department of Biomedical Sciences, University of Sassari, 07100, Sassari, Italy. g: Istituto Nazionale Tumori IRCCS-Fondazione G. Pascale, 80131 Naples, Italy. * Corresponding Author; andrea.ronchi@unicampania.it.*

Background

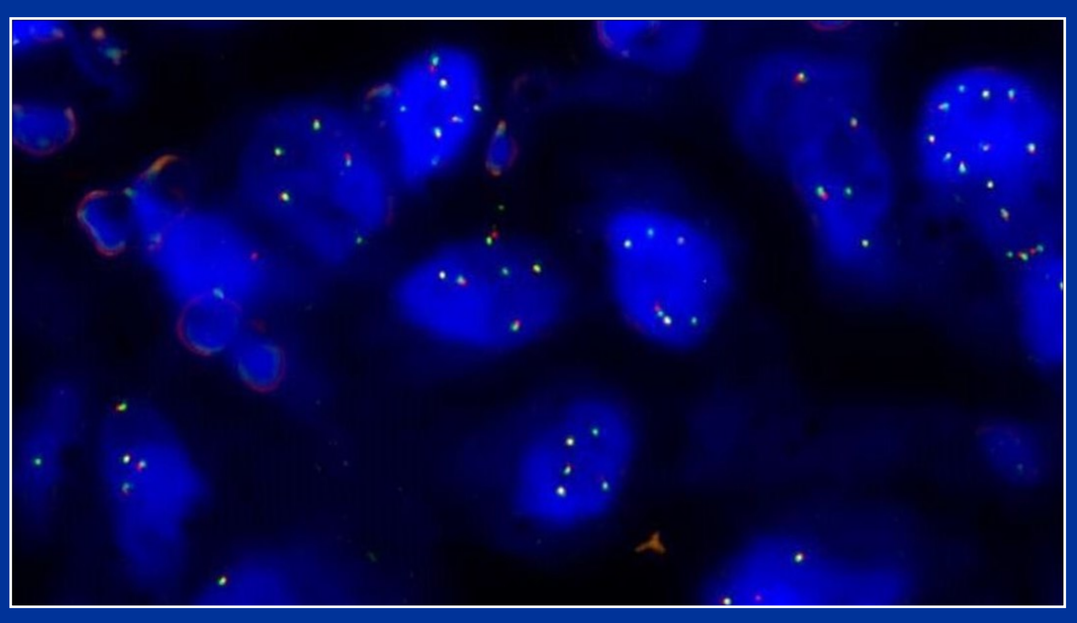
Malignant Cutaneous angiosarcomas (cASs) are aggressive neoplasms, with high metastatic rate and high mortality (1). Patients affected by cASs have few therapeutic chances, such as surgery and radiotherapy, while chemotherapy is not very effective. Two subtypes of cASs are defined, with different clinical and molecular features: primary cAS and secondary cAS. The molecular landscape of cASs is still poorly known. The role of MYC in cASs is still debated, but it seems to be hyperactive in these neoplasms, probably due to epigenetic mechanisms (2).

Methods

Twenty-nine formalin-fixed and paraffin-embedded tissue samples of cASs were collected by 4 Italian centers (University of Campania "Luigi Vanvitelli", University of Sassari, University of Catania, Oncological National Institute "Pascale"). Molecular analysis was performed by using TruSight™ Oncology 500 (TSO500) targeted hybrid-capture based NGS assay. TSO500 is designed to detect multiple classes of mutations including single-nucleotide variants, multi-nucleotide variants, small Insertions / Deletions, microsatellite instability and tumor mutational burden. Fluorescence in-situ hybridization (FISH) was performed to detect MYC amplifications and translocations. Immunohistochemistry (IHC) was performed to indagate the expression of c-myc and FGFR4 proteins.



MYC immunohistochemistry (left) and FGFR4 immunohistochemistry (right)



FISH showing MYC amplification

Results

c-Myc IHC was tested in all 29 cases. Twenty-one (72.4%) cases showed stained cells, while no stained cells were observed in the remaining 8 (27.6%) cases. Positivity was defined as at least 30% of positive cells. Eleven out of 29 (37.9%) cases resulted positive, and the remaining 18 (62.1%) cases resulted negative. The 11 positive cases included 6 (54.5%) primary cASs and 5 (45.5%) secondary cASs.
FISH was tested in 25 cases MYC amplification was present in 5 (17.2%) cases, including 3 (60%) primary cASs and 2 (40%) secondary cASs. MYC rearrangement was observed in 1 (3.4%) case, corresponding to a secondary cAS. One (3.4%) case, corresponding to a secondary cAS, showed both MYC rearrangement and amplification. Moreover, a copy number gain was observed in 2 cases. MYC amplification and/or rearrangement significantly correlated with secondary cAS ($p<.05$).
NGS revealed some recurrent mutations in cASs. In particular, FGFR4 G388R, RUNX1 L56S and MUTYH G393D mutations resulted in 46.8%, 50% and 33.6% of cases, respectively.
All cASs showed FGFR4 expression by IHC, but expression intensity was lower in FGFR4-mutated cases ($p<.05$).

Conclusions

c-myc deregulation is a frequent event in cASs, but its molecular basis is largely unknown, as wel as the molecular landscape of these rare neoplasms. In our series, c-myc was overexpressed in 37.9% of cases, including both primary and secondary cASs. Although myc overexpression was originally reported in secondary cASs, data suggest a role for myc also in primary forms. MYC amplifications and rearrangements by FISH are less frequent, demonstrating that other different molecular mechanisms may lead MYC deregulation. Interestingly, MYC amplification and/or rearrangement significantly correlated with secondary cAS ($p<.05$). NGS was performed to further explore the molecular landscape of cASs. NGS analysis revealed some recurrent mutations with potential clinical significance in cASs, including FGFR4, RUNX1, MUTYH. In particular, FGFR4 G388R mutation was present in 46.8% of cases. The clinical significance of FGFR4 G388R is 'Pathogenic' on ClinVar (Variation ID: 16326) and has been reported in different solid neoplasms such as breast carcinoma. This mutation has been associated with poor prognosis, including resistance to chemotherapy and early disease relapse in breast carcinoma (3). The report of FGFR G388R in cASs could be important, as Pan-FGFR inhibitors like PRN1371, TAS-120 and INCB054828 are being evaluated in patients with solid tumors harboring FGFR alterations. FGFR4 G388R enhances STAT3 signaling and correlates with higher MAPK pathway activation (4). In our series, FGFR4 G388R significantly correlated to a lower expression of FGFR4 protein, suggesting that FGFR4 mutation may lead to decreased protein expression. An epigenetic link between FGFR4 alteration and MYC deregulation needs further investigation.

References

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