

Subcutaneous symplastic haemangioma after radiotherapy: A case report

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SUMMARY

Symplastic haemangioma is a rare vascular tumor presented with regressive and degenerative atypia in stromal cells. Its morphology represents a challenge in classification of vascular tumors, regarding their biological behaviour in particular. We present a case report of a 47-years-old female with a history of left-sided breast adenocarcinoma treated by resection followed by adjuvant chemotherapy and radiotherapy. Three years after the primary diagnosis a tumorous mass appeared in the region of upper margin of left scapula, in subcutaneous tissues and the trapezius muscle. Histologically, the tumor was formed by multiple blood vessels of varied diameter and wall thickness. Endothelial lining was bland, without atypia; thromboses were observed in vascular spaces. In the interstitium, a population of spindle and pleomorphic cells with distinctive atypia and bizarre nuclei was found. These cells showed positivity in immunohistochemical expression of smooth muscle actin, further extensive immunohistochemistry including cytokeratins was negative. Mitoses were absent, proliferating activity was minimal. Signs of infiltrative growth pattern were not found and the tumor lacked hallmarks of malignant behaviour. A diagnosis of symplastic haemangioma was established. Above mentioned atypical stromal cells show myofibroblastic and sporadically smooth muscle differentiation. Their atypical appearance is associated with degenerative alterations similar to changes in leiomyomas with bizarre nuclei or ancient schwannomas. Etiopathogenesis of these changes is not clear, there are hypotheses considering long-lasting persistence of the lesion, regression of ischaemic or postinflammatory origin, or, like in our case, postirradiative degeneration. Differential diagnosis of symplastic haemangioma is widespread and contains many histological entities of variant histogenesis and biological potential. For proper classification, an extensive investigation including immunohistochemistry, clinical and anamnestic data and imaging methods is necessary.

Keywords: symplastic haemangioma – ancient changes – pleomorphic cells – bizarre nuclei

Symplastický hemangiom v podkoží po adjuvantní radioterapii: kazuistické sdělení

SOUHRN

Symplastický hemangiom je vzácná cévní léze, která se prezentuje přítomností regresivních změn a degenerativních atypií ve stromálních buňkách. Svou morfologií vyvolává diferenciálně diagnostické rozpaky v klasifikaci cévních nádorů a jejich zařazení z hlediska biologických vlastností. Presentujeme případ 47leté ženy s anamnézou resektce levého prsu pro adenokarcinom, s následnou chemoterapií a radioterapií. Tři roky od primární diagnózy došlo ke vzniku nádorového ložiska v oblasti horního pólu levé lopatky na rozhraní podkoží a musculus trapezius. Histologicky se jednalo o nádor tvořený cévami různého kalibru a širé stěny. Endotel cév byl blandní, bez atypií, v lumen cévních prostor byly trombózy. V intersticiu byla zastížena populace vřetenitých a pleomorfních buněk s výraznými atypii a bizarními jádry. Buňky vykazovaly pozitivitu v imunohistochemickém průkazu hladkosvalového aktinu, ostatní extenzivní imunohistochemické vyšetření, včetně průkazu cytokeratinů bylo negativní. Mitózy nebyly zastíženy, proliferativní aktivita byla minimální, známky infiltrativního růstu nebyly pozorovány. Nález byl interpretován jako symplastický hemangiom, nádor postrádal známky maligního chování. Popsané atypické stromální buňky mají myofibroblastickou a někdy i hladkosvalovou diferenciaci. Jejich atypický vzhled je přikládán degenerativním změnám obdobným jako v leiomyomech s bizarními jádry, či ancientních schwannomech. Etiopatogeneze těchto změn není zcela jednoznačná, zvažuje se souvislost s dlouhodobým přetrváváním léze, regresivní změny ischemického, či pozánětlivého původu, nebo, jako v našem případě, po radiční terapii. Diferenciální diagnóza symplastického hemangiomu je široká a zahrnuje množství jednotek různé histogeneze a biologických vlastností. Pro správnou klasifikaci je proto nezbytné extenzivní vyšetření včetně imunohistochemie, klinických, zobrazovacích a anamnestických dat.

Klíčová slova: symplastický hemangiom – ancientní změny – pleomorfní buňky – bizarní jádra

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CASE REPORT

We present a 47-years-old female patient with three years long history of left breast cancer (adenocarcinoma NST, grade 2,

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pT1c, pN1c, hormonal receptors positive, without ERBB amplification). Patient underwent mastectomy with axillary lymphadenectomy following by adjuvant chemotherapy and radiotherapy targeting to the region of left thoracic wall. Three years after the primary diagnosis, at a dispensary examination, a tumorous mass was found by physical and radiological examination. The tumor was located in the subcutaneous soft tissue near the upper margin of left scapula, on the border of subcutaneous fat and the left trapezius muscle. By the ultrasonography, a hypoechogenic, well circumscribed tumor was described; the largest diameter of the nodule was 33 mm. CT scan was performed 2 months before resection. In this examination a tumor was seen, with nonhomogenous and hypodense foci in the centre (suspected tumor desintegration) and with dense stripes

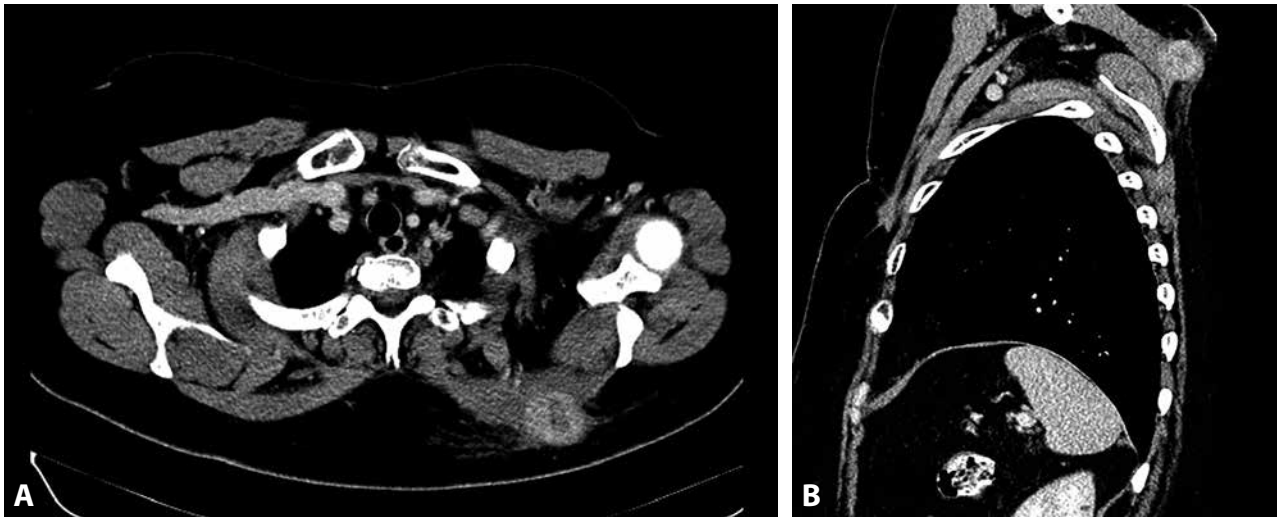


Fig. 1. CT scan. Round shaped tumor with nonhomogenous and hypodense structures (arrow). Dense stripes penetrating to the surrounding tissues. **A:** Transversal section. **B:** Sagittal section.

penetrating to the subcutaneous fat (Fig. 1). Radiologic differential diagnosis was widespread, primary or secondary tumors were considered including a metastasis of formerly diagnosed breast carcinoma. A diagnostic core cut biopsy was performed. In three core biopsy samples a mesenchymal proliferation with regressive and degenerative changes was found. The biological behaviour of the proliferation was controversial, so a surgical resection of the whole mass was highly recommended.

For the definitive diagnosis, we obtained a surgical specimen sized 55x40x45 mm, containing skin on the surface and a part of skeletal muscle. On sagittal cut surface, a nodular tumor was observed at the interface between subcutaneous fat and muscle. The tumor was soft, elastic, pale pinkish coloured, of porous consistence, partly hyperaemic. The largest diameter of the tumour after formalin fixation was 25 mm (Fig. 2).

Histologically, a regressively changed vascular tumor, composed of variably shaped vessels was present. Small thin-walled vessels, capillaries, as well as larger blood vessels with thick muscular wall and lumen dilatation were observed. The vascular spaces were lined by flat uniform endothelial cells



Fig. 2. Macroscopic evaluation of the specimen. Porous hyperaemic tumor, well circumscribed, on interface between subcutaneous fat and trapezius muscle.

without atypia. Many vessels were occluded by thromboses, some of them with organisation and recanalisation. The interstitium was edematous, with sparse chronic inflammation, hemosiderosis and distinctive exudation of fibrin, but not affecting the blood vessels' walls. Interstitial cells were spindle shaped, some of them were atypical and pleomorphic with bizarre nuclei, many of these elements were multinucleated. Infiltrative growth was not observed and the surgical resection was radical (Fig. 3).

Extensive immunohistochemistry was performed, particularly to identify the histogenesis of the pleomorphic interstitial cells. These cells showed partial positivity by labelling for smooth-muscle actin. Other smooth-muscle (desmin, h-caldesmon) and vascular (CD31, CD34) markers (Fig. 4), as well as macrophage markers (CD68, CD163), markers for neurogenic differentiation (S100 protein, SOX10, GFAP, CD57) and for perivascular epitheloid cells (HMB-45, Melan-A) were negative. The proliferation activity, evaluated by the Ki-67 immunohistochemistry (MIB-1), was up to 2 % of tumor cells. Staining for Pan-cytokeratines (MNF 116, AE-1/AE-3) did not reveal epithelial structures, so the metastatic origin from formerly diagnosed breast carcinoma was excluded. According to the morphology and immunohistochemistry and in the correlation with anamnestic data, we established the diagnosis of symplastic haemangioma. Furthermore, a molecular analysis of the tumor tissue was performed. Mutations in the gene for fumarate hydratase (*FH*) by the one-step PCR and DNA sequencing were investigated, but no mutation in all 10 exons of this gene was detected.

DISCUSSION

The presence of cellular and nuclear atypia in histopathology of vascular tumors leads to diagnostic difficulties when estimating their possible malignant potential. Atypia in endothelial cell is generally considered a sign of malignancy and aggressive behaviour. However, atypia in stromal cells is more likely a manifestation of regressive and degenerative changes. Pleomorphism of stromal cells and pseudosarcomatous appearance of vascular lesions represent a diagnostic trouble. The symplastic changes may occur in several types of vascular tumors, particularly in arteriovenous haemangiomas and malformations, infantile or capillary haemangiomas (4-6).

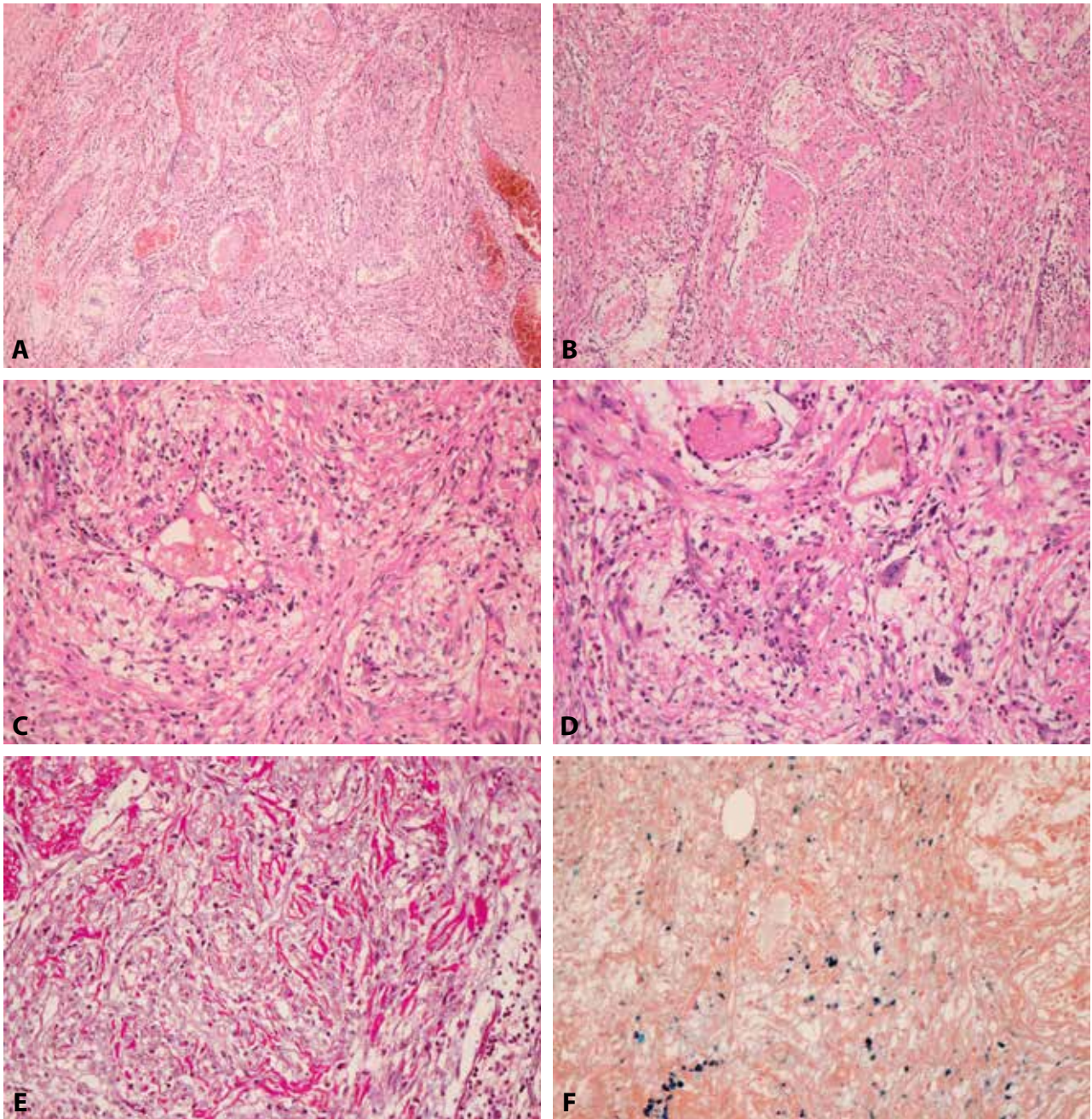


Fig. 3. Histopathologic evaluation. **A:** Vascular tumor with variable vascular spaces (HE, 100x). **B:** Thrombotic obliteration of blood vessels (HE, 200x). **C, D:** Spindle stromal cells with addition of atypical pleomorphic cells (HE, 400x). **E:** Dense stromal fibrin exsudation (Masson's trichrome, 400x). **F:** Disperse hemosiderosis (proof of iron by Pearls' reaction, 400x).

Histopathologic appearance of symplastic haemangioma is represented by vascular spaces of variable gauge and wall thickness. All the spaces are lined by flat endothelial cells, without atypia, or increased mitotic activity. A spindle cell population is present in the interstitium, showing mainly myofibroblastic, rarely smooth muscle differentiation. In this cellular population, variable proportion of large pleomorphic and atypical cells is observed, frequently multinucleated, with hyperchromatic and bizarre nuclei. Despite of atypical morphology, the cells lack marks of increased proliferation, mitotic activity is minimal and atypical mitoses are not present. Other signs of malignancy, such as necrosis or infiltrative growth, are also absent. Mild disperse interstitial inflammation could be present, represented by lymphocytes, plasma cells, macrophages and mastocytes (4,7).

Morphologically, atypical changes in symplastic haemangioma are similar to degenerative atypia found in other mesenchymal and neurogenic tumors. Pleomorphic histology is often observed in ancient schwannomas, or bizarre leiomyomas (leiomyomas with bizarre nuclei, LBNs) (7). The name „symplastic“ represent multinucleated syncytial structures, exactly like in LBN, which historically carried the name symplastic leiomyoma (4,7).

Occurrence and origin of degenerative atypia in symplastic haemangioma as well as in other tumors of similar histology have not been exactly clarified. Long-lasting persistence of a minimally proliferating tumor may stand in the background of the cellular and nuclear atypia. Therefore, the term „ancient changes“, first used in evaluating and classification of schwannomas, is an appropriate designation (8,9). Other hypotheses tend towards ischaemic or post inflammatory etiology of atypia

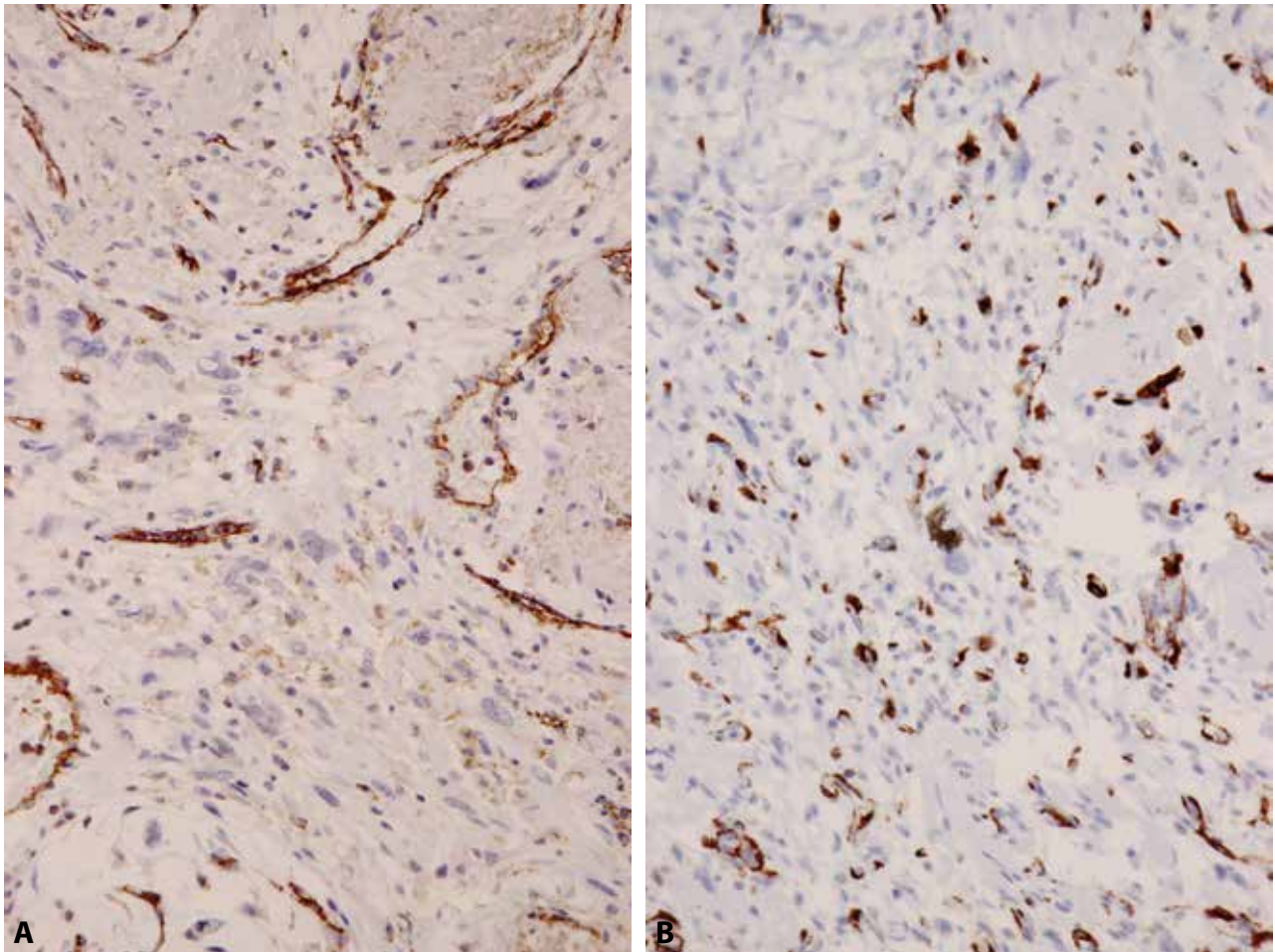


Fig. 4. Immunohistochemistry. **A:** Immunolabelling for CD31 (positivity in endothelial cells, atypical stromal elements negative, 400x). **B:** Immunolabelling for smooth muscle actin (disperse positivity in atypical stromal cells, 400x).

in primary lesions (10). Of further pathogenetic causes, postradiation changes should be mentioned (as it was in our case), hormonal influences, or changes induced after haemangioma treatment by propranolol (6,7,11). That is also the reason, why some authors (7) favour the name ancient haemangioma for this entity.

Published reports of symplastic haemangioma are quite rare, and there is not much known about genetic background of this tumor. Several studies analyzed tumors of similar histological features, particularly smooth muscle tumors. Subtypes of LBN with unique genetic changes were identified, especially with mutations in fumarate hydratase gene (*FH*) (12-14). According to recent studies, *FH* mutations are strongly associated with hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) (15,16). This association is not known in case of symplastic haemangioma and data regarding *FH* gene mutation testing in this tumors are absent. In our case, we did not prove mutation in *FH* gene.

There is a discrepancy between the number of published cases and expected incidence of symplastic haemangiomas, according to above mentioned hypotheses of their origin. The reason may be the broad differential diagnosis of symplastic haemangioma, because there are several lesions similar in morphology and immunophenotype. This tumor is often misinterpreted as pleomorphic angioleiomyoma, cutaneous angiomylipoma with pleomorphic change or other pseudosarcomatous mesenchymal or neurogenic entities, such as the above mentioned ancient schwannoma (7). Furthermore, multinucleate

cell angiohistiocytoma (MCA) (17) and pleomorphic hyalinizing angiectatic tumor (PHAT) may be considered in differential diagnosis (18). Excluding of malignant vascular neoplasms, or another cancer of mesenchymal or neurogenic histogenesis, is essential (19). For correct classification of symplastic haemangioma a combination of precise gross and histopathologic analysis, including sufficient tissue sampling and extensive immunohistochemistry, is necessary. Correlation with surgery, imaging methods and proper anamnestic data of the patient, including previous oncological treatment, is helpful.

CONCLUSION

Symplastic haemangioma belongs to a category of tumorous lesions presenting with cellular and nuclear pleomorphism, but lacking other signs of malignant behaviour. Atypia in these lesions are generally of degenerative and regressive origin and these neoplasms show minimal or no proliferation activity. Symplastic haemangioma should be considered in the differential diagnosis of lesions with so-called ancient changes. Sufficient tissue sampling, extensive immunohistochemistry, anamnestic data, surgical point of view and imaging methods are essential for the correct diagnosis.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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