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Abstract

Introduction. Angiosarcomas (AS) arising from vascular tissue, accounting for 3.3% of all sarcomas, have a poor prognosis. Radiation-induced AS is a rare late complication of radiotherapy treatment and is characterized by a gene expression profile such as amplification of the MYC oncogene, by which we can distinguish primary from the secondary induced tumor. Case report, At 77-year-old patient, with early-stage endometrial adenocarcinoma, the radical hysterectomy with bilateral salpingo-oophorectomy was initially done. According to pathological risk factors, the postoperative external beam conformal radiotherapy (CRT) of the pelvis was administered with concomitant brachytherapy. Six years after the treatment, on the anterior abdominal wall, in the region of the postoperative irradiation field and surgical scar, an infiltrative angiosarcoma of the skin and subcutaneous adipose tissue, was histologically confirmed. The patient received six cycles of mono-Adriamycin chemotherapy with verified partial regression. Additional immunohistochemical analysis (IHH) of c-MYC, Ki67 and CD34 expression showed a high proliferative index (Ki67 around 60%) and c-MYC positivity indicating the molecular pattern of radiation-induced AS. Furthermore, the high proliferative index could explain a good response to chemotherapy. Conclusion. The novel postoperative radiotherapy techniques provide better survival and local control in risk-endometrial cancer groups with a decrease of irradiation complications. These patients with longer survival, are in a higher risk of developing radiation-induced tumours as late side-effects of radiotherapy. When assessing the probability of radiation-induced AS, IHH analysis of c-MYC expression could distinguish secondary from others AS if Cahan’s criteria are fulfilled.

Key words: Cahan's criteria, MYC, angiosarcoma, radiotherapy, secondary malignancy.

Apstrakt

Uvod. Angiosarkomi (AS) čine 3.3% svih sarkoma i imaju lošu prognozu. Zračenjem indukovani angiosarkomi su retka kasna komplikacija lečenja radioterapijom a karekterišu
se posebnim profilom genske ekspresije, poput amplifikacije c-MIC onkogena, pomoću kojeg možemo razlikovati primarni od sekundarno indukovanog tumora. **Prikaz slučaja.** Kod pacijentkinje stare 77 godina, sa adenokarcinomom endometrijuma u ranom stadijumu, inicijalno je urađena radikalna histerektomija sa bilateralnom adneksektomijom. Prema patohistološkim određenim faktorima rizika, indikovana je postoperativna radioterapija karlice uz brahiterapiju. Šest godina nakon radioterapijskog tretmana na prednjem trbušnom zidu, u regiji postoperativnog oziljka i zračnog polja histološki je potvrđen infiltrativni angiosarkom kože i potkožnog masnog tkiva. Pacijentkinja je primila šest ciklusa hemoterapije mono-Adriamicinom sa verifikovano delimičnom regresijom. Dodatna imunohistohemijska analiza (IHH) ekspresije c-MIC, Ki67 i CD34 pokazala je visok proliferativni indeks (Ki67 oko 60%) i pozitivnost c-MIC što ukazuje na molekulski obrazac AS-a izazvanog zračenjem, a visok proliferativni indeks mogao bi objasniti dobar odgovor na hemoterapiju. **Zaključak.** Nove tehnike radioterapije omogućavaju bolje preživljavanje i lokalnu kontrolu pacijenata sa karcinomom endometrijuma visokog rizika. Međutim produženo preživljavanje ove pacijente stavlja u povijest rizik od razvoja tumora izazvanih radiacijom kao i drugih kasnih efekata radioterapije. Kada se procenjuje mogućnost pojave radiacijom indukovanog AS-a, dodatne IHH analize ekspresije c-MIC-a mogu pomoći u razlikovanju sekundarnih od ostalih AS-a ako su ispunjeni Kanovi kriterijumi.

**Ključne reči:** Kanovi kriterijumi, MYC, angiosarkom, radioterapija, sekundarni maligniteti.

**Introduction**

Angiosarcoma (AS) is rarely occurring malignancy that arises from vascular tissue and has a poor prognosis. The incidence of all soft tissue sarcomas in Europe ranges from 3.3 per 100,000 in Eastern Europe to 4.7 per 100,000 in Northern Europe and it is reported that 3.3% of all sarcomas are angiosarcomas. By site AS are divided as follows: soft tissue AS, bone AS and cutaneous AS. Furthermore, cutaneous AS are divided as scalp and face AS, AS in the contest of lymphedema (Stewart-Treves syndrome), epithelioid AS and radiation-induced AS.
AS is characterized by diverse but recurrent chromosomal abnormalities and mutations of genes involved in angiogenesis and endothelial cell receptors. The patterns of mutation are so distinct that it could distinguish secondary, mostly radiation-induced AS from primary tumours.

The first set of criteria used for the diagnosis of radiation-induced malignancy (RIM) were established by Cahan et al. in 1948. Today a modified Cahan's criteria are used that encompasses the following: i) Radiation-induced malignancy must arise in the boundaries of the irradiation field; ii) Duration of the latent period between proposed induced malignancy and previous irradiation must be greater than 4 years; iii) Primary malignancy and induced malignancy must be biopsied and must be of different histology, iv) The tissue from the induced malignancy arose must be metabolically and genetically normal before irradiation.

From a molecular point of view around 100 genes are deregulated during secondary AS development including upregulation of MYC, KIT and RET genes, as well as concomitant upregulation of MYC and FLT4 and downregulation of CDKN2C gene. Similar genetic patterns are present in other radiation-induced tumors suggesting the distinct tumorigenic mechanism of radiation.

In our study, we analyzed the clinical problem of distinguishing the primary from secondary-radiation induced angiosarcoma by immunohistochemical analysis of c-MYC and other markers expression in the case of a patient with endometrial cancer treated with adjuvant radiotherapy.

Case report

Clinical features

The patient was 77 years old with no prior or family history of malignancy. Initial staging workups revealed endometrial adenocarcinoma UICC FIGO 1C. According to the protocol the patient underwent radical hysterectomy with bilateral salpingo-oophorectomy in November 2011 in Military medical academy (MMA) in Belgrade. Histopathology (PH)
findings confirmed endometrial adenocarcinoma FIGO Ic (pT1c), infiltrating the uterine wall to a depth of more than 1/2 myometrium.

According to multidisciplinary board decision, adjuvant conformal external beam radiotherapy (CRT) of the pelvis was administered. A total dose of 45 Gy in 25 fractions was given (5 days per week) in MMA radiotherapy department while three applications of intracavitary brachytherapy were performed at Institute for oncology and radiology of Serbia, in the period January-March 2013. Treatment-related early toxicity during RT treatment included diarrhoeas and tenesmus which was successfully medically treated.

In March 2019 a patient underwent surgical excision of clinically suspicious multiple cutaneous tumors in the region of surgery scar and irradiated area of the anterior abdominal wall in the general hospital in Kraljevo. Initial PH findings were characterised as mesenchymal malignancy. Further immunohistochemical (IHH) analysis revealed infiltrative angiosarcoma of skin and subcutaneous fat tissue with R1 posterior resection margin.

Further diagnostic workup which included an MRI of the abdomen detected a soft tissue tumour of the anterior abdominal wall with no further spreading. The patient underwent six cycles of systemic chemotherapy including mono-Adriamycin (75mg/m2) with good partial response (Figure 1).

**Pathological and IHH analysis**

Specimen of skin measured 105x40x30mm was sent. On the cross-section, we revealed fields of haemorrhage in subcutis.

Sections of 4µ thickness were sampled. Standard histological analysis was performed using standard Hematoxylin and Eosin-staining. Sections revealed a tumour in the deep portion of the dermis and fat tissue. Tumour consists of malignant fusiform cells arranged in pseudovascular channels. Neoplastic cells had hyperchromatic nuclei and numerous mitotic figures.

The same blocks of tissue, previously prepared for classical pathohistology, were used for immunohistochemical analysis.
We performed IHH staining for CD34 (Ventana, RTU, clone QBEnd/10), Ki67 (Ventana, RTU, clone 30-9, RTU) and c-MYC (clone 9E10.3).

Staining for CD34 and Ki67 was performed in immunostainer- BenchMark GX, Ventana. C-MYC was stained manually. For c-MYC identification, the demasking procedure was used as the first step in the IHH procedure. For antigen unmasking, a 10mM citrate buffer (pH6) was used for 21 minutes in a microwave oven at the maximum power of 800W. The sections were then washed with TBS (TRIS (hydroxymethyl) aminomethane buffer saline) and incubated with the primary c-MYC monoclonal antibody (Thermo Fisher Scientific Invitrogen, MA5-12080, clone 9E10.3) diluted at 1:50 ratio. The sections were treated by using the commercial Thermo Scientific UltraVision Quanto Detection System HRP DAB (TL-060-QHD). Immunoreactions were subsequently developed by using DAB (diaminobenzidine) as a chromogen. The sections were counterstained with Mayer's haematoxylin.

The quality and the specificity of the developed immunoreactions were controlled by negative controls performed by omitting the primary antibody and applying TBS instead.

CD34 immunoreactivity showed the vascular origin of the tumour. Nuclei of malignant cells had a high proliferative index (Ki67 around 60%). C-MYC protein expression was shown in numerous positive tumour cells (Figure 2.).

**Discussion**

Secondary AS occurs as radiation-induced, but also in patients with chronic lymphoedema due to prior lymphadenectomy (after breast surgery) or in patients that have a chronically altered lymph drainage for other reasons (i.e. Stewart-Treves syndrome) 7.8.

Radiation-induced secondary malignancies are rare but important late side effects of radiotherapy (RT) and have an impact on optimal treatment decision-making especially with expected survival longer than 5 years.

The adverse effects of radiation vary depending on the technique and dose applied and they are generally divided into early and late adverse effects. Early toxic effects of radiation on healthy tissue are due to acute inflammation (radiation colitis, cystitis, radio-dermatitis etc).
On the other hand, the late adverse effects are caused by micro-vascular damage, chronic inflammation and radiation-induced genetic instability. Whereas early adverse effects are reversible and have a good prognosis when treated medically, late effects are permanent and generally are less responsive to medications or lifestyle changes.

The development of contemporary RT techniques such as CRT (4 field box-technique) and intensity-modulated radiotherapy (IMRT) have improved target dose coverage and reduced early and late treatment toxicities\(^a\). Some studies, however, found no reduction of gastrointestinal and genitourinary toxicities of radiation when CRT is used and even suggested a positive correlation between the development of early and late toxicities in organs which receive a relatively high dose of radiation during the CRT treatment \(^{10,11,12}\).

Nevertheless, contemporary radiation techniques (CRT and IMRT) made possible escalation of treatment dose which increased the number of long-term cancer survivors, patients at increased risk of developing late adverse effects of radiotherapy including RIM\(^b\).

Endometrial carcinoma is one of the most common gynecologic malignancies worldwide, with standard treatment protocol in early operable stages which includes radical hysterectomy followed by adjuvant radiotherapy if postoperative histology assesses risk factors for local recurrence (high-grade carcinomas or deep myometrial and cervical stroma invasion) \(^{14,15}\). Adjuvant RT provides a significant improvement of local control and disease-free survival after 5 years of 90\% for intermediate-risk patients and around 80\% for high-risk patients (high-grade tumors or myometrial invasion) \(^9\). In our patient, the adjuvant RT was performed due to microscopic invasion of more than half of myometrium to achieve better local control (according to hospital protocol at the period).

Modern CRT allows more precise irradiation of a targeted volume, with an sparing effect on normal tissue, however with these techniques a larger volume of normal tissue is irradiated with a lower dose. RIM arises mainly in the irradiated tissue or the nearby tissues due to collateral radiation exposure \(^{17,18}\). A large cohort study by Chaturvedi et al. has shown that after radiation treatment of gynecological malignancies (external beam RT and brachytherapy) there is a secondary malignancy incidence increase of 12\% compared with the cohort that did not receive radiation treatment. RIM was detected with a median follow up of 12.2 years. The most common RIM observed were anal, colo-rectal and
gyneceological malignancies. Concerning endometrial carcinoma treatment, (PORTEC)-1 trial showed that 22% of the patients that received RT developed secondary neoplasm after 15 years, while 16% of non-irradiated patients developed secondary neoplasms.

In several clinical series, comparing c-MYC gene amplification and expression between secondary AS of the skin and primary AS showed that c-MYC expression is statistically significantly more prevalent in secondary AS. Also, a c-MYC expression is present in secondary angiosarcoma associated with chronic lymphedema (Stewart-Treves sy). Nevertheless, in a minority of primary skin angiosarcoma c-MYC expression could be found too as well as in primary AS of other sites.

The study by Styring et al. underlined the role of MYC, KIT and RET genes upregulation in the pathogenesis of radiation-induced AS and its diagnostic application as a basis for therapeutic use of kinase inhibitors in these sarcomas. This study also found that over 100 genes are significantly deregulated between primary and secondary angiosarcomas, for example: upregulation of FLT4 a tyrosine kinase receptor for vascular endothelial growth factor and other vascular-specific receptor tyrosine kinases, like TIE1, KDR and FLT1. This somatic mutation pattern could be of diagnostic importance since it is common in radiation-induced sarcomas and other radiation-induced malignancies.

In the end, it should be noted that the overall prognosis of radiation-induced AS is poor. Although surgical treatment is the therapy of choice in other sarcomas, it seems that re-occurrence of the AS, including radiation-induced ones is high, even when radical excision is made. This could be explained by the multifocality of the tumour so truly negative resection margin is hard to be achieved. Haematogenic spread in lung, pleura and bone as well as spread to regional lymph nodes are possible. At the time, Doxorubicin-based chemotherapy remained the standard treatment for metastatic or unresectable AS, but other chemotherapeutic agents such as Taxanes showed activity against AS. Overall response rates to chemotherapy are variable from 20% to 60%. In our patient high proliferative index (Ki67 around 60%) and c-MYC positivity could explain a good response to chemotherapy.

Target therapy could be a potential new approach in the treatment of radiation-induced AS such as tyrosine kinase inhibitors sorafenib, brivanib and sirolimus, as well as KIT inhibitor
imatinib, anti-VEGF antibody bevacizumab and thalidomide but the experience is still limited and further studies are necessary."

**Conclusion**

The development of novel radiotherapy techniques provided longer survival and better local control of high-risk endometrial cancer. Longer survival of these patients put them in a higher risk of developing RIM and other late side-effects of RT. When assessing the probability of radiation-induced AS, IHH finding of c-MYC expression could help to distinguish secondary from others AS if Cahan’s criteria are fulfilled. Additional IHH analysis to other molecular markers such as KIT or RET kinases and VEGF expression could be of diagnostic and therapeutic importance, in the era of target therapy in oncology.

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Figure 1. Clinical presentation of angiosarcoma in our patient:

Clinical presentation initially, before chemotherapy with mono-ADM (left) and after chemotherapy (right).
1. Neoplastic cells arranged in poorly formed vascular spaces (HE, X 400); b) CD34 immunostaining-positive tumor cells (IHC, x400); c) Ki67 immunostaining- high proliferative index (IHC, x400); d) c-MYC immunostaining-numerous positive tumor cells (IHC, x400).