Case Report

Multifocal Superficial Rapidly Growing Postirradiation Sarcoma Mimicking Metastatic Carcinoma

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Abstract

Radiation induced sarcomas (RIS) on cytology is rare however need to be reported as they are histologically distinct from the primary tumor and arise years after completion of the radiotherapy. Fine needle aspiration cytology is mostly indicated in cancer patients suspected of recurrence/metastasis and rarely in secondary tumors post therapy or irradiation. Depending on the morphology and site of occurrence of RIS they can cause diagnostic difficulty with the primary carcinoma or sarcoma that was irradiated. Here we discuss a 49 yr old lady, known and treated case of carcinoma cervix who presented with multiple nodular swellings in the lower back and gluteal region and had clinical impression of metastatic carcinoma. The fine needle aspiration cytology smears revealed pleomorphic spindle shaped cells with abundant mitotic figures. Extensive immunocytochemical work up was done on the smear and cell block which helped to make a final conclusion of radiation induced pleomorphic sarcoma. The diagnosis of a tumor in a proven case of previous malignancy needs consideration of tumors secondary to therapy as well, along with the diagnostic differentials of metastasis or recurrence.

Keywords: *Mimicking metastasis, radiation induced sarcoma, squamous cell carcinoma*

Introduction

There has been an improvement in the overall and disease-free survival in most solid tumors with advancement in radiation therapy. However, every benefit comes for a cost; thus, the improved survival occasionally results in post-irradiation carcinomas and sarcomas. The radiation-induced sarcomas (RISs) are defined by the criteria as proposed by Cahan and Woodard[1] and modified by Arlen *et al*.:[2]

1. Treatment with therapeutic irradiation at least 3 years prior to the development of sarcoma
2. A sarcoma arising within the field of previous therapeutic irradiation
3. Differing histology between the sarcoma and the primary tumor that required radiotherapy.

The tissue at the edge of radiation receives a sublethal dose (<30 Gy) which causes genomic instability as compared to the lethal dose which kills the tumor cells. These irradiated cells with defective DNA repair mechanism accumulate further mutations and progress to develop secondary carcinomas and sarcoma. The risk factors for developing RIS are genetic predisposition (Li–Fraumeni syndrome, retinoblastoma, and neurofibromatosis), treatment during young age, high-dose irradiation, and simultaneous use of chemotherapy (alkylating agents). RIS is a rare complication of radiation for carcinoma breast, cervix, oral cavity retinoblastoma, and Hodgkin's lymphoma. The different histological subtypes of RIS as reported in literature are undifferentiated pleomorphic sarcomas (most common), angiosarcoma, leiomyosarcoma, fibrosarcoma, osteosarcoma, and less commonly liposarcoma, whereas the most common carcinomas occurring postirradiation (radiation-induced carcinomas [RIC]) are lung carcinoma followed by

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esophagus and breast. RISs after the treatment of carcinoma cervix are osteosarcoma, angiosarcoma, and malignant fibrous histiocytoma/pleomorphic sarcoma.[3]

Majority of the anticancer therapy includes radiotherapy; hence, it is critical for clinicians to be aware of RICs/RISs which can occur years after radiotherapy. Any suspicious growth in such patients should be biopsied and if a second malignancy is detected it has to be treated as a primary malignancy and treated accordingly. In cases of RIS, the treatment is surgical resection with negative margins.

Case Report

A 49-year-old female presented to the cytology outpatient department with multiple nodular swellings ranging from 0.5 to 2 cm in the lower back around the gluteal region. The nodules had come up within 1 month and were rapidly increasing in size [Figure 1a]. The clinical diagnosis was metastatic carcinoma, as the lady was a known and treated case of carcinoma cervix Stage IIIA with radiotherapy (treated elsewhere, so the details were not available) in 2012. Fine-needle aspiration (FNA) from these firm lesions yielded scanty particulate material, and the smears showed moderately pleomorphic spindle-shaped cells. We suspected it to be a spindle cell squamous cell carcinoma (SCC) because of the history of cervical carcinoma and applied pan cytokeratin (CK) and P63 immunostains on the smears, both of which were negative. No further workup could be done because of paucicellularity; hence, we did not categorize the malignancy. However, the patient came back to us after 2 weeks, and this time, the existent lesions had become almost double the size with bleeding and many more new lesions [Figure 1b]. We repeated an FNA cytology (FNAC) with extra material for cell block. The repeat smears were particulate and very cellular. The tumor cells showed a much bizarre morphology as compared to the previous smears with numerous typical and atypical mitotic figures [Figure 1c-e and Figure 2a and b]. This time around we suspected a pleomorphic tumor and started with the sarcoma immunohistochemistry (IHC) panel [Pan CK – Figure 2c, vimentin, S 100, smooth muscle actin, CD31, desmin]. Only vimentin was positive, whereas all the other markers were negative. Hence, we tried the second panel of antibodies (CD34, CD99, Bcl2, MyoD1, FLI 1, CD30, Melan A, EMA, CD117, and cyclin D1). to our surprise, only CD99 [Figure 2d] showed diffuse membranous positivity, whereas the cyclin D1 showed diffuse nuclear positivity and all other markers were negative. Hence, we reported the case as radiation-induced pleomorphic sarcoma. The cell block had enough material; hence, no biopsy was attempted from the lesion. The vaginal vault was healthy and other metastatic workup was negative. The oncology team had planned for surgical excision of the lesion; however, the patient was lost to follow-up.

Discussion

The cytology report should address whether the tumor is a recurrence/metastasis or a second new tumor. One of the diagnostic problems is that many of the primary carcinomas have areas of sarcomatous differentiation (renal cell carcinoma, SCC with spindle morphology, transitional cell carcinoma, and seminoma), which on recurrence can be confused with a RIS. The second problem is the epithelioid morphology of the sarcoma (RIS), which can be confused with recurrence or metastasis of a primary carcinoma.

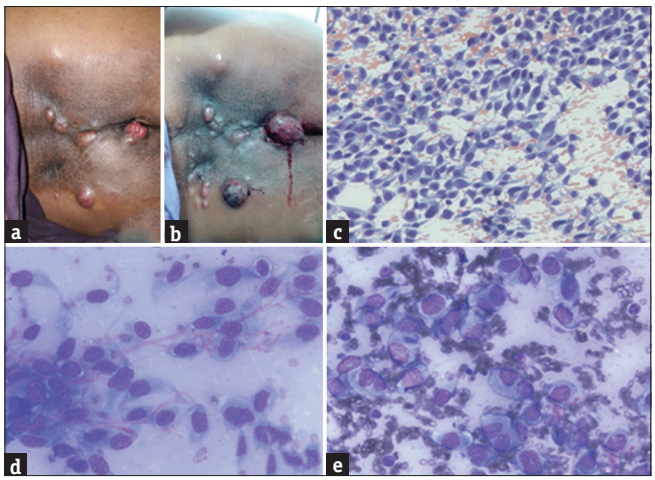

Figure 1: (a and b) Clinical image of the tumor 2 weeks apart – marked increase in size and number of lesions. (c-e) The Papanicolaou (c: PAP, ×200) stain and May–Grunwald–Giemsa (d and e: MGG, ×400) stain showing the cellular smears with tumor cells having oval-to-round shape with cytoplasm ranging from bipolar to epithelioid appearance

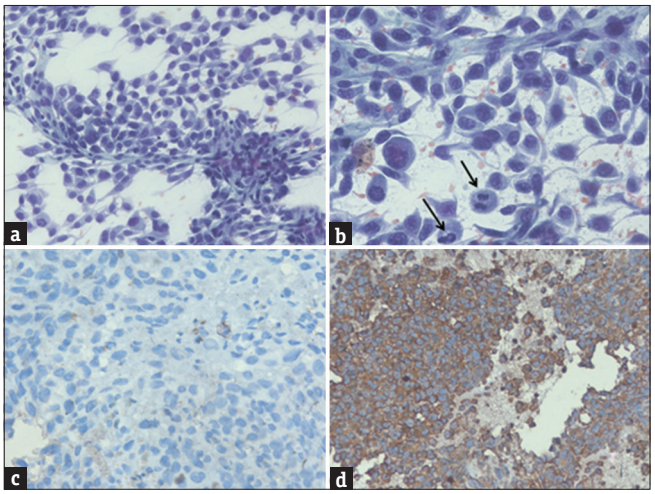

Figure 2: (a and b) The Papanicolaou (c: PAP) stain highlighting the moderate pleomorphism with brisk mitotic figures (arrow). (c and d) The immunohistochemistry stain of Pan cytokeratin being negative (c: ×200) and strong diffuse membranous staining of the tumor cells with CD 99 (d: ×200)

Any pleomorphic malignancy can mimic a sarcoma; hence, a battery of low- and high-molecular CK along with diffuse strong positivity for epithelial membrane antigen (EMA) can be useful to establish a diagnosis of carcinoma. In addition, P63 IHC positivity can also be helpful to confirm a carcinoma, as it is almost never seen in sarcomas.[4] In the index case, the tumor cells showed spindled-to-pleomorphic appearance which can be seen in primary and metastatic SCC (spindle cell variant); however, the nuclear features, the multinucleated tumor giant cells, and IHC profile (Pan CK, EMA, and P63 all negative) were against SCC.[5] Melanomas and large cell lymphomas can display varied morphology from spindle to round to bizarre with prominent nucleoli and hence should always be considered in the differentials of any sarcoma.[6] Hence, a melanoma (HMB45/Melan A) and lymphoma (CD30) IHC marker should be added to the panel of any pleomorphic tumor. The clinical presentation of the present case was also unique because of the multifocality of the tumor with satellite lesions which is usually described in lymphoma[6] and melanoma[7] and is not common in sarcomas. Although radiation-induced pleomorphic sarcomas are known, such an aggressive tumor needs pathological approach from all possible ways to exclude the less common RIS. The malignancies that need to be considered here are the superficial subcutaneous and multifocal malignancies (epithelioid sarcoma, angiosarcoma, Kaposi sarcoma, dermatofibrosarcoma protuberans, leiomyosarcoma, malignant melanoma, cutaneous anaplastic large cell lymphoma, and myeloid sarcoma), the postirradiation sarcomas[3] (angiosarcoma, pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, rhabdomyosarcoma, and extraskeletal osteosarcoma), and the sarcomas positive for the following immunohistochemical profile (vimentin, CD99, and cyclin D1). However, with the history of radiation and rapid growth, the morphology of tumor cells and marker profile, the only tumor that was fitting was the extra skeletal osteosarcoma with the closest differential diagnosis of pleomorphic sarcoma. Both tumors can be positive for all the three above markers. One more difficulty that we would like to highlight is the limited sampling that we get in FNAC, which can easily miss out any differentiated sarcomatous areas or heterologous component such as osteoid and cartilage. The diagnosis of pleomorphic sarcoma is by exclusion based on IHC and molecular workup. Some of the factors that are presumed to play a role in RIS are the age at exposure, the dose and time since radiation, and the genetic susceptibility. Radiation remains one of the established causes of bone and soft-tissue sarcomas, especially in children who carry the maximum risk of RIS.[8] Kim *et al*.[9] found that (25/33 pts) 78% of the RIS were females and the median age was 55 years with a median latency of 12 years; however, this patient had developed the sarcoma after 5 years of treatment. The most common primary malignancy in their study was carcinoma breast (9/33 cases) followed by carcinoma cervix (8/33) as the second most common cause. The median dose of primary therapy was 50.4 Gy; however, in this case, the dose of radiation could not be documented. The most common site of RIS was trunk (only 6/33 cases were superficial location) and the two common subtypes of RIS were osteosarcoma followed by pleomorphic sarcoma. Many studies have proven that the clinical outcome of RIS is worse as compared to sporadic sarcomas.[10-12] RISs are treated by surgical excision; however, the results have been dismal because of the complete surgical excision that is not always possible, as most RIS are deeply located; second, the surgical planes are distorted by the previous radiation. RIS can also be treated with repeat radiation; however, the dose is dependent on the concern for complications of reradiation.[11,12]

Conclusion

The diagnosis of a tumor in a proven case of previous malignancy needs consideration of tumors secondary to therapy as well, along with the diagnostic differentials of metastasis or recurrence. Although RIS has poor outcome, a surgical approach can be attempted with curative intent. This case highlights that RIS can be multifocal, superficial and needs a battery of markers to confirm the histological subtype. In addition, this case proves that FNAC with cell block can be good enough for confirmation or categorization of such tumor.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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