

Squamous Cell Carcinoma vs Radiation Induced Sarcoma: confusion under the microscope

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Introduction

The purpose of the pathology department is to provide accurate diagnoses with the objective of avoiding misdiagnosis. In the case of a 59-year-old woman who had a recurrent chest wall mass excised after radiation therapy. The specimen was misdiagnosed as a radiation induced sarcoma which was later changed to recurrent squamous cell carcinoma. This was done by utilizing comparative studies with previous biopsies and thorough case review, through interdepartmental conferences, which illuminated the true state of the poorly differentiated tumor. This case highlights factors which complicate the diagnostic process, as well as, brings to light the preanalytical and analytical steps that should be taken to improve the final accuracy of any diagnosis.

Pertinent Patient History

A 59-year-old woman presents to her doctor with an increasing mass beneath her right chest wall. Patient has a history of multiple squamous cell carcinomas including one that previously required a right anterior chest wall soft tissue resection with a free flap reconstruction several years prior.

On 12/05 the new mass was biopsied with the suspicion of radiation induced sarcoma. 7 sections were biopsied including two primary tumor sections, anterior right shoulder, right mid clavicle, superior sternum, inferior sternum, right lateral upper arm; as well as, one primary tumor section for intraoperative analysis were sent to the pathology department for confirmation diagnosis. The final diagnosis for the biopsies and frozen section was recurrent squamous cell carcinoma.

On 02/06 surgical resection of the right anterior chest wall was performed that included the removal of ribs 1 through 7, portion of sternum, lung parenchyma, visceral pleura, and pericardium. The original diagnosis at the time was a sarcomatoid carcinoma with features of undifferentiated pleomorphic sarcoma involving bone, cartilage, soft tissue, and skin.

On 02/07 concerns were raised about the difference in diagnosis between prior biopsies and the final diagnosis made after resection. 20 more sections were taken from the primary tumor and reviewed histologically by multiple pathologists before the final diagnosis was changed to recurrent squamous cell carcinoma which was consistent with prior biopsy diagnosis.

Pathological Findings

Gross Examination

The case was received in 14 parts, with the main excised mass present in the final part labeled as *right chest wall mass*. The specimen consisted of an oriented skin excision with attached soft tissue, ribs, sternum, lung parenchyma, pericardium and skeletal muscle that had a total measurement of 17.5 x 13.7 x 7.0 cm. A 6.5 x 2.3 cm pink tan, exophytic lesion was noted on the skin surface with a communicating 2.5 cm in diameter circular lesion (Figure 1). The specimen was differentially inked and serially sectioned. Sectioning through the mass revealed a circumscribed, pink tan, focally hemorrhagic and cystic cut surface that involved the majority of the underlying soft tissue extending from the lateral margin (Figure 2). The mass grossly involved the ribs. Gross photography was taken and representative sections were taken of the mass and mass invasion into adjacent tissue such as the ribs, pleura, pericardium, and skeletal muscle (Figure 2). The remaining parts included additional soft tissue margins for intraoperative consultation.

Histology

The original diagnosis published for the main right chest wall mass was sarcomatoid carcinoma with features of undifferentiated pleomorphic sarcoma involving bone, cartilage, soft tissue and skin. After interdepartmental review, the diagnosis was changed to focal residual squamous cell carcinoma with extensive sarcomatous differentiation. The mitotic rate was 14 per 10 HPF and necrosis was present, involving 20% of the sampled tumor. The margins on the main specimen were uninvolved by tumor and lymphovascular invasion was not identified. 11 out of the 13 additional margins and biopsies samples taken for intraoperative analysis demonstrated no evidence of malignancy. The remaining two, a superior sternal biopsy and an undesignated soft tissue biopsy, demonstrated focal involvement by carcinoma and focal cellular atypia (NEM), respectively. Both stated biopsies also had cautery artifact noted in the microscopic exam.

Ancillary Studies

After the routine H&E stains were examined, additional stains were ordered to elucidate the origin of the pleomorphic and poorly differentiated cells. The tumor was positive for vimentin and CD68 and negative for CAM5.2, panCK, EMA, CK903, p40, BER-EP4, S100, HMB45, actin, desmin, myoD1, myogenin, CD99, CD31, and CD34. Vimentin is a broad based stain that targets mesenchymal tissue and CD68 targets histiocytic tumors^{1,2}. The remaining stains were targeted for epithelial based tumors, melanocytic tumors and other sarcomas. Additional section taken later, however, did come back as positive for p40 which is a highly specific stain that targets squamous cell carcinomas (Figure 3).



Figure 1: 6.5 x 2.3 cm pink tan, exophytic lesion noted on the skin surface



Figure 2: Transverse section of primary tumor showing pink tan, focally hemorrhagic and cystic cut surfaces

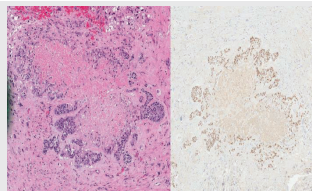


Figure 3: Positive p40 stain done from additional sections taken from primary tumor

Discussion

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer and typically arises on sun exposed tissue in older people, typically men (14% compared to 4-9% in women).^{4,5} Each year in the United States, at least 200,000 to 400,000 new cases of cSCC are expected, and disease-related death occurs in more than 3000 people with cSCC.⁵ The most widely accepted treatment for cSCC is usually surgical excision, but recurrence is relatively high with a 5-year recurrence rate of NMSC being 40.7% and after more than 1 it was 82%, according to cohort studies.⁵ cSCC previously fell into the broad category of non-melanoma skin cancer (NMSC) in which staging was primary determined by the size of the tumor; however, currently there is no staging protocol. The previous staging system was as follows;

- Stage I: tumor with a diameter of ≤ 2 cm
- Stage II: > 2 cm
- Stage III: based on clinical, histological, or radiologic evidence of one solitary node measuring ≤ 3 cm with lymphatic spread.
- Stage IV: tumor has directly invaded the axial skeleton, ≥ 2 lymph nodes affected, or distant metastasis.⁶

Radiation induced sarcomas (RIS) do not have a specific definition but are established based on three criteria that where proposed by Cahan and modified by Arlen et al.⁷ This includes (1) treatment with therapeutic irradiation at least three years prior to 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.⁷ Under these guidelines the original misdiagnosis for this case would appropriately fall under the radiation induced sarcoma umbrella. It has also been indicated that the most common histological subtypes of radiation induced tumors are squamous cell carcinomas.⁸ The latency period between radiation exposure and development of RIS has been estimated to be anywhere from 3 to 36 year, with the torso being the most common site of RIS development.⁷ Similar to cSCC the primary treatment option for dealing with RIS is surgical resection with caution when considering further post-surgical irradiation, due to concerns about toxicity.^{7,9}

In the hospital system the purpose of the pathology department is to provide accurate and timely diagnoses with the objective of avoiding misdiagnosis, for clinicians to appropriately treat and manage a patient's condition. In this case, the patient was misdiagnosed with a sarcomatoid carcinoma which is an aggressive variant of squamous cell carcinoma that recurs more often and is far more likely to metastasize with a poor survival rate.¹⁰ The discordance between the biopsy and excisional diagnosis prompted a review of the case by the pathology department. This caused the pathology department to go back and take more sections from the case which were then put through an interdepartmental review. Upon review, the final diagnosis was changed to recurrent squamous cell carcinoma. Avoiding misdiagnoses such as this is, not just the responsibility of the pathologist, but the Pathologist's Assistant (PathA), as well. Several crucial resources and techniques can be used to optimize best practices at the bench including;

- Proper protocol for the specimen
- Variable sampling from central and peripheral aspects of the tumor, as well as any heterogeneous areas that could demonstrate necrosis, calcification and hemorrhage
- Review of related operative report, patient history, radiographs, and prior pathology work-ups- specifically the prior biopsy of the tumor

These resources often demonstrate factors outside of the PathA's control that can complicate the case both macroscopically and microscopically including local infection, neoadjuvant treatment, or other patient genetic disorders. Steps a PathA can take to aid in the analytic examination of the specimen include requesting gross review with a pathologist, taking additional sections, taking more photographs, or even utilizing special preservation methods to save primary tumor for additional sampling, genetic studies, or molecular studies.

A Pathologist's Assistant is an integral part of a departmental team that has the goal of achieving accurate diagnoses. It is important not to become compartmentalized and complacent in the everyday work of specimen processing, a common trap for health care workers whose relationship with the patient is based on the tissue received at the bench. A specimen is not limited to the physical tissue but extends into the patient's history and the total clinical and pathologic work up that has led to the surgical excision. A complete understanding of the big picture of the patient's case is the major contributor to achieving the goal of improved patient diagnostics.

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