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A case of long term survival with skeletal only metastatic breast cancer

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ABSTRACT

INTRODUCTION: The prognosis of patients with metastatic breast cancer is very poor. Because of this, treatment of skeletal metastasis is often palliative with limited goals rather than cure. However, there are those patients, such as presented here, who survive for an extended time.

PRESENTATION OF CASE: This thirty-six year old female presented with lytic lesions to one ulna and rib five years after mastectomy for breast cancer. Despite radiation and chemotherapy, the ulnar lesion expanded and resulted in an elbow dislocation. The rib lesion was resected and the arm amputated above the elbow. She developed local recurrence in both her above elbow amputation stump and chest wall and a more proximal below shoulder amputation was performed with resection of chest wall lesion. Even though she had locally aggressive disease, she has survived for 31 years after diagnosis without any evidence of disease.

DISCUSSION: Reports of metastatic breast cancer survival indicate the five year survival to be 15%. There have been few reports indicating that those patients with skeletal only or oligometastatic disease have improved prognosis. It is not clear what biological properties of these tumors results in the improved survival.

CONCLUSION: This case highlights the challenges of giving patients the optimal treatment in the light of limited ability to predict prognosis. It also highlights the need to further investigate the phenotypes of breast cancer that can, despite metastatic disease and with modern treatment go on to long survival. In addition this case demonstrates the importance of long term followup.

1. Introduction

The prognosis of patients with metastatic breast cancer is in general very poor. The 5 year survival rate from the national cancer database has been reported to be 15% and the median survival rate is 8–24 months [1]. Many of these patients will referred for an orthopedic consultation because half of women who present with metastatic breast cancer at primary diagnosis will develop bone lesions [2]. Because of this the orthopedic treatment of skeletal metastasis for these patients is often palliative with the goal being relief of pain and restoration of short term function, rather than that of affecting a cure. However, there are those patients that despite the poor odds against them are able to survive.

2. Presentation of case

A thirty-six year old Caucasian female secretary presented to the orthopedic clinic in 1988 with a 9 month history of a painful, tender mass involving the midshaft of her left ulna. She reported that the pain was constant, worse with activity and only partially relieved by pain medication. She had a history of a modified left mastectomy for carcinoma of her breast in 1983, 5 years earlier. At that time she had two positive axillary lymph nodes which had been removed. Besides her mastectomy she was treated with 1.5 years of chemotherapy with vincristine, adriamycin and cyclophosphamide. She received no pre or postoperative radiation.

On presentation to the orthopedic office radiographs were obtained of her left forearm which demonstrated an osteolytic lesion involving 4 cm of the ulna. A chest X-ray, taken at the same time, revealed a similar osteolytic lesion in the left sixth rib with an associated pleural based mass. A true cut needle biopsy of the forearm tumor revealed an adenocarcinoma compatible with the diagnosis of metastatic breast carcinoma. It was decided at the time that the likelihood of a cure was remote. The patient therefore, received radiation treatment for each of these two skeletal lesions

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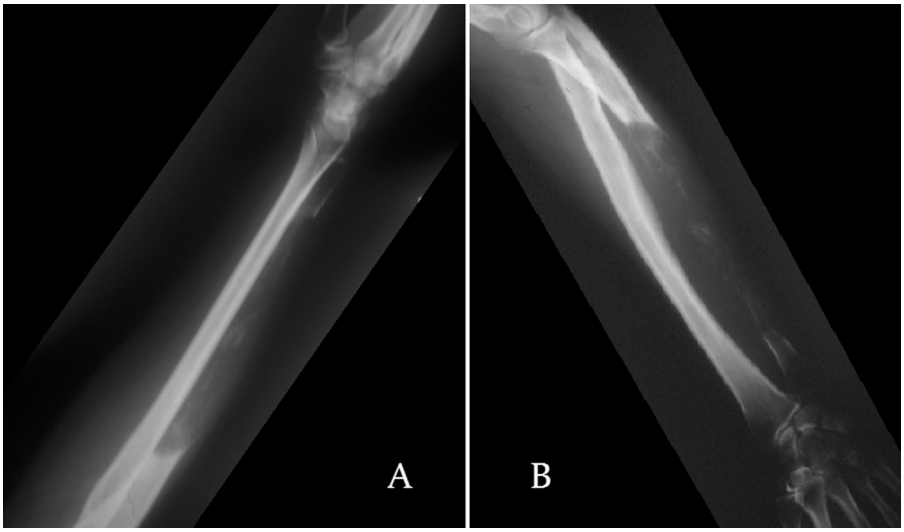

Fig. 1. (A) Lateral and (B) AP radiographs of the forearm demonstrating a large lytic lesion throughout the ulnar shaft caused by metastatic breast cancer.

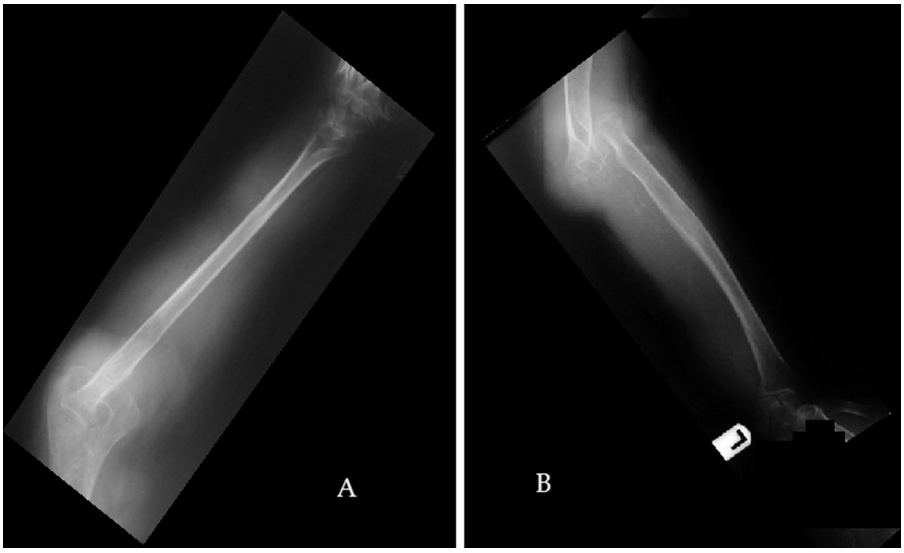

Fig. 2. (A) Lateral and (B) AP radiographs of the forearm demonstrating advancement of the lytic lesion despite radiation treatment resulting in dislocation of the radial – humeral articulation and significant pain with loss of function.

and was placed on Nolvadex. The patient returned to the office in 1992. She had significant relief for a few years after the second round of treatment but now the pain had returned in the forearm. Radiographs at that time showed that the tumor had advanced to destroy most of the ulna sparing only it's proximal few centimeters (Fig. 1) but the patient was feeling well and no plans were made for any surgical intervention. However, over the next year the tumor continued to advance destroying the entire ulna leading to dislocation of the elbow (Fig. 2). She developed severe pain in her forearm and significant disability due to the lack of left arm function. At that time she requested amputation of her arm.

To relieve symptoms and decrease the tumor burden a palliative above elbow amputation was performed in 1993. The mass was $15 \times 4 \times 4$ cm in size and resulted in destruction of the proximal ulna, invasion of the distal humerus and dislocation of the radius (Fig. 3). Recent histological analysis of retained specimens of her tissue was performed which demonstrated that the tumor was apocrine in morphology, positive for Her2 nu, and androgen receptor but negative for estrogen and progesterone (Fig. 4). In addition to her amputation, segments of two ribs were removed where her

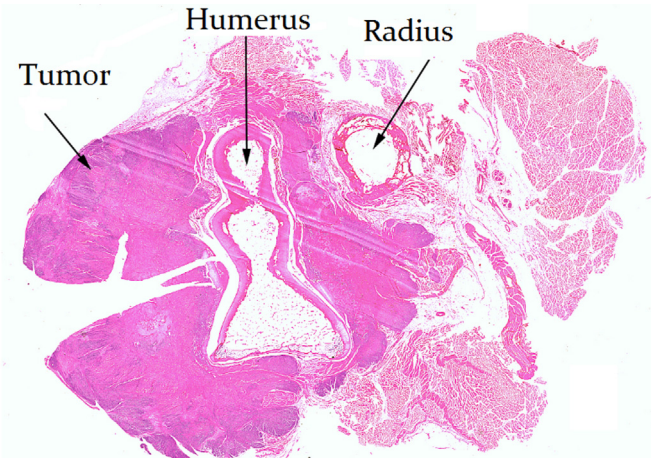

Fig. 3. H+E stained large mount sections of the proximal aspect of the forearm amputation. These slides demonstrate the significant size of the lesion and the dislocation that occurred at the elbow due to the mass.

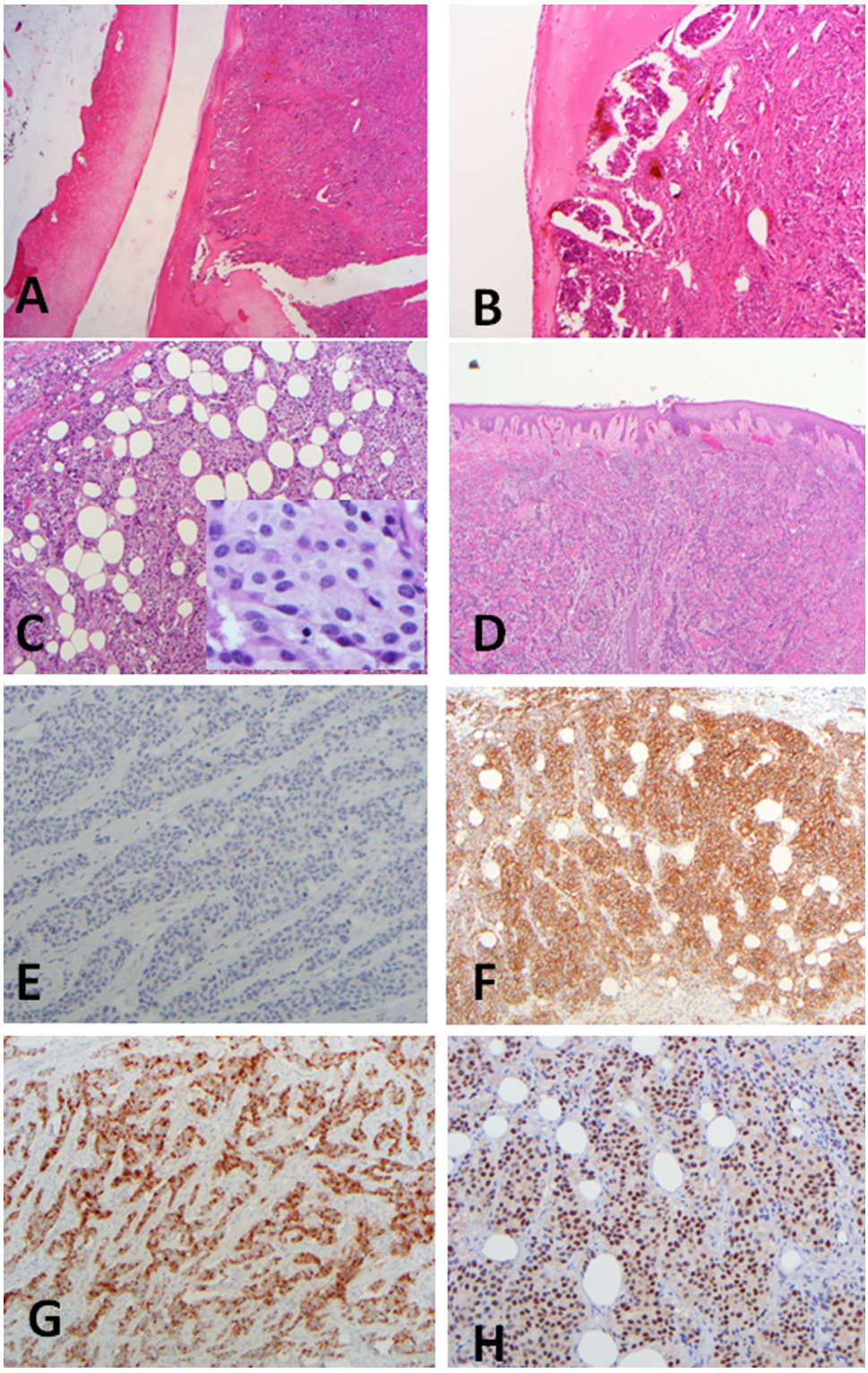

Fig. 4. Histopathology and immunostains of the tumor from the amputated limb with H+E; (A and B) tumor involves the bone ((A) 2×, (B) 10×); (C) tumor involves adipose tissue (10×), note the apocrine morphology of the tumor with conspicuous eosinophilic granular cytoplasm (inset, 60×); (D) tumor involves the deep and superficial dermis and sparing the epidermis (2×); (E) Estrogen receptor negative (10×); (F) HER2 positive with strong and complete membranous staining compatible with 3+ (10×); (G) GCDFP-15 positive staining (10×); (H) Androgen receptor positive (10×). The morphology and immunoprofile are compatible with HER2+ apocrine type mammary carcinoma.

second and only other lesion was identified. She was treated with vinblastine, doxorubicin, thiotepa, and halotestin (VATH) as well as tamoxifen. Despite this treatment, three years after the amputation, she developed a recurrent mass in her above elbow stump. A below shoulder amputation was performed in 1996 (Fig. 5). An $8 \times 6 \times 4$ cm tumor mass in the soft tissues to the anterior humerus as demonstrated on histology. The bed of the rib resection was also re-excised since she had developed a recurrence in her chest wall. Novantrone, citovorin and 5 FU were added to her regimen for an additional round of chemotherapy. After her surgery she was also

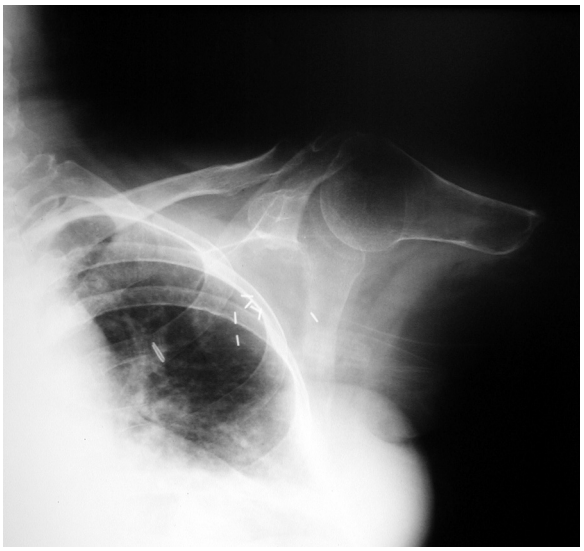

Fig. 5. AP radiograph of the shoulder demonstrating the above elbow amputation.

Table 1
Timeline for clinical case.

1983	Mastectomy and 2 nodes removed age 31 years
1988	Diagnosed with skeletal metastasis to ulna and rib: radiation and chemotherapy
1992	Above elbow amputation with rib resection
1996	Below shoulder revision amputation with revision rib resection
2014	No evidence of disease at age 62: patient reports that she is not significantly disabled years since radical mastectomy and 18 years since last operation

placed on Arimidex. She had not returned to the clinic after her chemotherapy and we had presumed that she had passed away.

Follow up on the patient 26 years after being first seen with metastases in her left ulna and 6th rib we were pleased to find that she was doing exceptionally well (Table 1). It is now 31 years since her left breast mastectomy and 18 years from her below shoulder amputation and rib re – resection and she is now without recurrence. She is now 62 years old, and in good health. She wears a cosmetic left arm and works in her original job as a secretary with the aid of a computer and reports not to feel significantly disabled.

3. Discussion

This case is one of only a limited number of reports with long term follow-up on patients surviving metastatic breast cancer and highlights the challenges of treating these patients and other patients with metastatic disease. This case also demonstrates the value of long term follow-up as emphasized by Codman and coworkers [3,4]. He argued for his "end result idea" as a "common sense idea" in that every hospital should follow every patient for a long enough time to determine whether or not the treatment had been successful and then to inquire, if not, why not. The goal was to prevent similar failures in the future and determine what different courses of action might be better for patients in the future. For this patient, given her status on presentation with metastatic breast cancer lesions 5 years after mastectomy and chemotherapy it was a reasonable course of action at that time to offer her palliative radiation. However, if we had been better able to predict the outcome that she has had with very long term remission and possibly a cure we may have treated her differently. With an earlier resection of the lesion we may have been able to salvage her arm and hand or at least save her arm to her elbow.

In reviewing this case 31 years after initial diagnosis of breast carcinoma we considered what might the prognostic indicators that could have suggested a survival advantage for her been. While her age on presentation and her biomarker profile without the availability of Herceptin would also make us think that she would have a poor prognosis. We believe that the limited, skeletal only location for her late recurrent disease could be a positive prognostic factor. There have been others who have argued that patients with oligometastasis or limited lesions, such as hers, may represent a population who will go on to have more favorable outcomes and would benefit from more aggressive treatment with curative intent [5–7] and there are reports that support this. Greenburg et al. reports that at a mean of 15 years follow up 1.8% of patients with metastatic breast cancer following combination chemotherapy achieved complete responses into a disease free state. They also described that the long term surviving group were of a younger age, had a lower tumor burden but did not comment on metastatic lesion sites [8]. Kobayashi et al. report a case series of 30 year experience with aggressive multidisciplinary treatment of breast cancer with relapse free rate of 42% at 20 years with patients with metastasis to a single organ [9]. Ziaei et al. reported that patients with breast cancer skeletal metastasis vs. other site metastasis has a slight survival benefit [10]. Milano et al. reported 85 metastatic lesions in 40 breast cancer patients treated with Stereotactic Body Radiation Treatment, achieving a 4-year overall survival of 59%. They found that the most favorable prognostic factor for breast oligometastatic patients was metastases only involving bone [11].

Breast cancer has a natural tendency to metastasize to bone. 70% of breast cancer patients develop bone metastasis [12]. The molecular mechanism of tumor growth in bone has been elaborated extensively and involves the receptive and supportive bone microenvironment [13]. Much of the molecular data regarding bone metastasis highlights the invasive phenotype that is acquired during this transition argues against any more positive outcome with skeletal metastasis [14]. It has been hypothesized that that in order to metastasize breast cancer must undergo an epithelial to mesenchymal transition that increases its tropism to bone and increases its aggressive nature [15]. Other phenotypic changes such as expression of RANK and MMP may affect the capacity of the cells to metastasize and generate osteolytic lesions [16] and may be specific to those tumors that are active in bone. The specific prognostic benefit of skeletal only metastasis may simply be that the lesions have an unknown affinity to bone which would cause debilitation but not mortality the same way vital organ metastasis would.

We were able to complete immunohistochemistry on samples that had been saved in the department of pathology from our patient's initial amputation but not from her primary breast excision which is one limitation on identifying the primary tumor molecular profile [17]. The tumor has an immunoprofile of $AR^{+}/ER^{-}/PR^{-}/Her2/neu^{+}$ and morphology of apocrine carcinoma. These tumors usually have distinct apocrine molecular signature [18]. This type of tumor has recently been described through screening breast carcinoma with AR staining [19]. It is expected that the driving force for the tumor's behavior will mainly be related to the HER-2/neu overexpression and expected to be aggressive [20]. Therefore, this tumor was expected to have worse outcome, particularly with the lack of target therapy of trastuzumab on diagnosis. We did see significant local aggressiveness but no further metastasis despite significant tumor burden. This may indicate that other markers specific to metastastatic potential may be better for predicting long term survival in patient's such as ours.

4. Conclusion

Here, we present a case of a patient with skeletal only metastatic breast cancer and long term follow-up with extensive relapse free

survival. This case reinforces the importance of giving patients reasonable treatment options that give them the best chance at survival and if they do, the best chance at a good functional result. This case also demonstrates that there is still much that is left to be learned about the phenotypes of metastatic breast cancer that when treated with the appropriate therapies may result in a cure. For some cases, more aggressive treatment may be more beneficial than for others. However, at this point we have limited ability to determine which few patients will go on to survive their metastatic cancer. It is our conclusion that at this time the patients who may benefit from further attention to the possibility of curative intention and more aggressive orthopedic intervention are those who have had one or two lesions detected at greater than 3 years after initial diagnosis when the primary site has been removed. This case of long term follow up reminds us that there are in fact patients with significant disease free periods from metastatic breast cancer that deserve a unique treatment plan aimed at maintaining function.

Conflict of interest

All authors do not have any conflicts of interest with regards to the contents of this submitted article.

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Consent

Written informed consent was obtained from the patient for this case report and accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal on request.

Authors contribution

All authors participated in data collection, analysis, writing and editing of the manuscript.

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