ABSTRACT
We describe a patient with metastatic metaplastic sarcomatoid carcinoma of the breast who achieved a complete clinical response to anthracycline and alkylating agent based chemotherapy. Fifteen months later, she developed acute myeloid leukemia with mixed leukemia lineage (MLL) gene rearrangement. The leukemia relapsed after standard induction therapy with idarubicin and cytarabine. Salvage chemotherapy failed and she succumbed to neutropenic sepsis.

INTRODUCTION
Metaplastic carcinoma of the breast has been recognized as a distinct clinicopathological disease since 2000. Microscopically these tumors show features of both epithelial and mesenchymal malignancies. Metaplastic sarcomatoid carcinoma (MSC) of the breast is a type of metaplastic carcinoma with overt carcinomatous and sarcomatous features apparent under the light microscope. It is a rare disease and accounts for less than 1% of all breast malignancies.

We describe a patient with metastatic MSC of the breast who had a complete clinical response to doxorubicin and ifosfamide containing regimen. Fifteen months after beginning chemotherapy, she developed therapy related acute myeloid leukemia (M5) with mixed lineage leukemia (MLL) gene rearrangement. The leukemia proved to be resistant to multiple chemotherapy regimens and the patient finally succumbed to complications of neutropenic sepsis. The MSC of the breast remained in remission till her death.

CASE REPORT
The patient was a forty year old Hispanic female who initially presented in 2007 with a large mass involving her right breast. Core biopsy of the mass revealed a malignant neoplasm with sarcomatoid features. Computed tomographic (CT) images of her chest, abdomen and pelvis showed no sites of metastases. She subsequently underwent a modified radical mastectomy of her right breast. Pathological exam of the mastectomy specimen showed an eight centimeter, biphenotypic tumor with components of invasive ductal carcinoma (Fig.1a) and a high grade chondrosarcoma (Fig.1b). The sarcoma component stained positive for vimentin, desmin and S-100 (Fig 1d). The epithelial (carcinoma) component stained positive for pankeratin (Fig 1c) and cytokeratin 7. Stains for Her 2, estrogen and progesterone receptors were negative. Sentinel lymph node was not involved. She declined adjuvant chemotherapy and received radiotherapy to her chest wall to a total dose of 54 grays.

Figure 1a. Carcinomatous component of the tumor. H&E X 200
Figure 1b. Sarcomatous component of the tumor. H&E X 200
Figure 1c. The carcinoma cells are positive for Pank-keratin stain.
Figure 1d. The chondrosarcoma cells are positive for S-100 stain.

Fourteen months after her diagnosis, she presented with cough, fever and pleuritic chest pain. CT scan of her chest now showed a lobulated, fluid filled mass involving the lower lobe of the left lung (Fig 2a). A CT biopsy of this mass showed a poorly differentiated carcinoma consistent with the breast primary. No other sites of metastases were visible on imaging studies.

She received six cycles of chemotherapy employing doxorubicin (50mg/m2), ifosfamide (5000mg/m2) and Masna. Cycles were repeated every 21 days. Repeat imaging studies after completing chemotherapy showed complete resolution of the lung mass (Fig 2b).

Fifteen months after being diagnosed with stage IV cancer, she presented with gingival hyperplasia and a diffuse petechial rash involving her trunk and extremities. Complete blood count showed a hemoglobin of 5.1gms/dl, while white blood cell count of 14,000/mcl and platelet count of 15,000/mcl. Peripheral smear showed numerous monoblasts. Bone marrow biopsy and aspi-
rate confirmed acute myelocytic leukemia (M5) (Fig 3a, 3b). Flow cytometry showed the blasts to express CD4, CD11b, CD13, CD33 and CD65. CD 14 was not expressed. Cytogenetic studies showed a reciprocal translocation of chromosome 9p22 and 11q23. Fluorescent in situ hybridization probes confirmed rearrangement of the MLL gene. CT scans of her chest, abdomen and pelvis showed no evidence of metastatic cancer.

She was diagnosed with therapy related acute myeloid leukemia, M5. Induction chemotherapy employing idarubicin and cytarabine in standard 7+3 fashion was administered. She achieved a morphological complete remission and then received consolidation with high dose cytarabine. The leukemia relapsed six months after completing consolidation. Salvage chemotherapy with mitoxantrone/etoposide, daclizumab and clofarabine failed. Palliative care was initiated. Thirty months after being diagnosed with metastatic MSC of the breast, she died of neutropenic sepsis and cerebral mucormycosis, while still in remission from her breast malignancy.

Figure 3a. Bone marrow core biopsy shows 100% cellularity with involvement by acute monoblastic leukemia. H&E X 40

Figure 3b. Flow cytometry dot plots show the acute leukemia to co-express CD64 and CD15 which is typical of AML-M5.

DISCUSSION

MSC of the breast has been felt to be an aggressive tumor with poor prognosis. A retrospective review from the Mayo clinic had suggested a median survival of 7-8 months after the diagnosis of metastatic disease. Hennessy et al retrospectively reviewed 100 patients with MSC of the breast at MD Anderson cancer center. They noted a median survival of twelve months in patients with metastases. There is no consensus as to the optimal management of these patients and the same principles used to manage invasive breast carcinoma's are commonly used in their treatment.

By light microscopy these tumors are a composite of a high grade

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sarcoma and an invasive carcinoma. Hence rationally designed treatments have been attempted targeting these two components. We administered a commonly used sarcoma regimen of doxorubicin and ifosfamide to our patient with metastatic disease. This led to a sustained remission of her metastatic tumor for thirty months. In the MD Anderson series, the authors noted that three patients with MSC of the breast who had received adjuvant doxorubicin and ifosfamide had not recurred after a median followup of fifty-five months. Brown-Glaberman et al used a sarcoma regimen with ifosfamide and etoposide in a patient with stage IV metaplastic breast carcinoma. They noted a 38% reduction in the size of the metastatic deposits.

The carcinoma component of MSC of the breast usually does not express estrogen or progesterone receptors, or Her-2/neu. Platinum compounds have shown promising activity in such “triple negative” invasive breast cancers. Mehta et al used a combination of carboplatin and albumin bound paclitaxel in a patient with stage IV metaplastic breast cancer and noted a clinical complete remission which lasted twenty months.

Our case report is unique in that our patient achieved a durable complete remission of her metastatic disease with a commonly used sarcoma regimen. Her death, thirty months after being diagnosed with lung metastases, was not related to progressive cancer, but to therapy related acute leukemia. Acute leukemia with MLL gene rearrangement is a well known complication of prior therapy with topoisomerase II inhibitors, including aniracylencines. This is the first case report describing the development of this leukemia, in a patient with stage IV MSC of the breast.

REFERENCES