

INTRODUCTION

Diffuse intravascular coagulation (DIC) is associated with 6.8% of solid tumors, with common laboratory findings including thrombocytopenia, hypofibrinogenemia, and elevated D-dimer - development of DIC is associated with inferior survival. Breast cancer itself is an independent risk factor related to occurrence of DIC (1). Bone marrow metastasis resulting in DIC has been identified in other cancers - anti-DIC treatments alone may not improve DIC and successful recovery involves chemotherapy (2). Only a small proportion of solid tumors will present with acute DIC as an initial manifestation of the tumor (3).

Few cases have been identified regarding management and outcomes of metastatic breast cancer as a primary cause of cytopenias by diffuse bone marrow involvement. Diagnosis involves identifying diffuse carcinomatous bone marrow infiltration, though leukoerythroblastic peripheral blood smear is also suggestive. One institutional study suggested that only 0.17% of patients present in such a way. Median survival is between 19-20 months. Thirty-eight percent of such cases are associated with ER+/PR- cancers, and patients most at risk are those with intermediate-high grade breast cancers. While cytopenias may necessitate dose delay and reductions, they do not usually pose major issues during treatment (4).

CASE DESCRIPTION

A 33-year-old female with history of bipolar disorder presented with one month worsening mucocutaneous bleeds and lower extremity petechial rash. She denied recent illness. Family history was remarkable for a grandfather with hemochromatosis and a grandmother with breast and ovarian cancer. Physical exam was remarkable for dried blood in the bilateral nares, petechiae and ecchymoses on the bilateral lower extremities, and no appreciable hepatosplenomegaly or lymphadenopathy. Initial labs were remarkable for the below:

| Labs | Remarkable Values |
|----------------|---|
| CBC | Normocytic anemia with Hb 11.6 g/dL Platelet count 11,000/L Peripheral smear – unremarkable |
| BMP | Within normal limits |
| Liver function | ALP 266 U/L, ALT 308 U/L, AST 321 U/L |
| Iron studies | Iron 190, TIBC 263 with 73% saturation, ferritin 1947 |
| Other | INR 1.5, HIV nonreactive, hepatitis C RNA undetectable, ANA negative, direct antiglobulin testing negative, ADAMTS13 within normal limits |

Treatment was initiated for immune thrombocytopenic purpura - however, her platelet count did not respond to steroids or IVIG, requiring romiplostim, rituximab, and multiple platelet transfusions throughout hospitalization. Hemochromatosis testing revealed C282Y and H63D mutations. Abdominal ultrasound was unremarkable.

The patient complained of worsening headache - CT brain showed acute subdural hemorrhage along the tentorium and posterior fissure (figure 1). The patient became febrile and CT scanning showed pulmonary infiltrates, an enlarged left axillary lymph node, left humeral lytic lesion, and bladder lumen air (figure 2). Antibiotic therapy was completed for cystitis and pneumonia.

Bone marrow biopsy showed poorly differentiated breast adenocarcinoma extensively replacing bone marrow. Axillary lymph node biopsy demonstrated triple negative poorly differentiated breast cancer. The patient was started on bisphosphonate therapy, gemcitabine, and carboplatin. BRCA testing was negative and next generation sequencing showed a TP53 mutation, concerning for Li-Fraumeni syndrome given early onset of breast cancer - she was, however, not tested for a germline mutation in the acute setting.

Figure 1: CT head without contrast with subdural hemorrhage

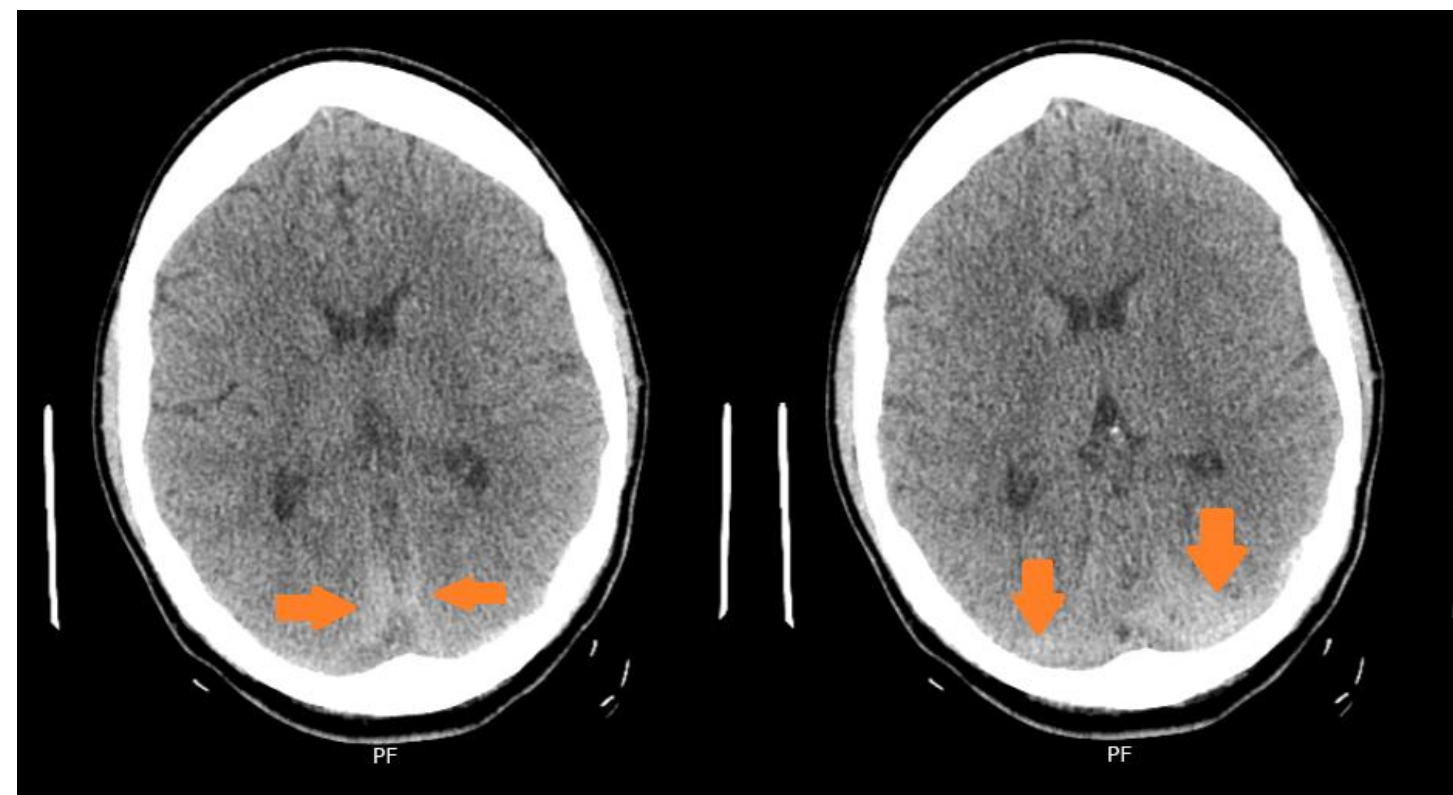


Figure 2: CT chest/abdomen/pelvis with (upper left to right) pulmonary infiltrates, axillary lymph node, humeral lytic lesion, and bladder lumen air

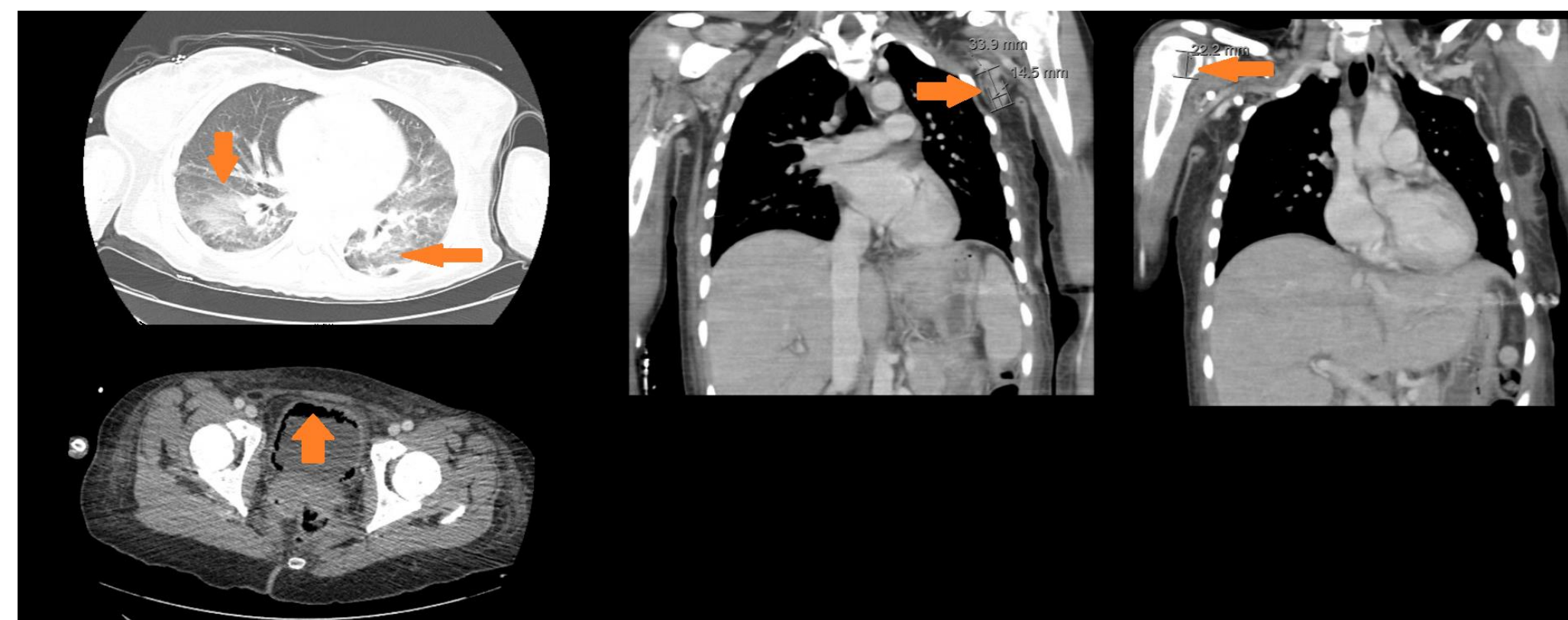


Figure 3: CT abdomen demonstrating areas of (right to left) splenic and renal infarcts

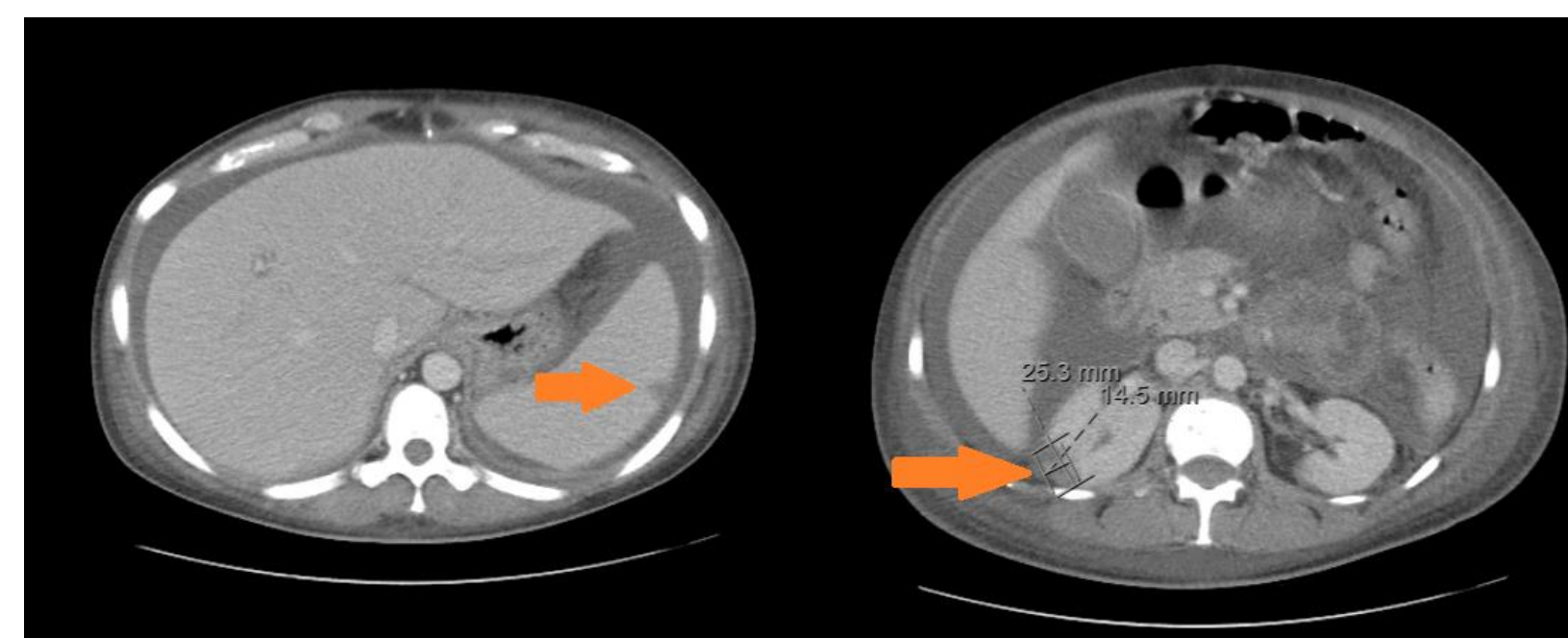
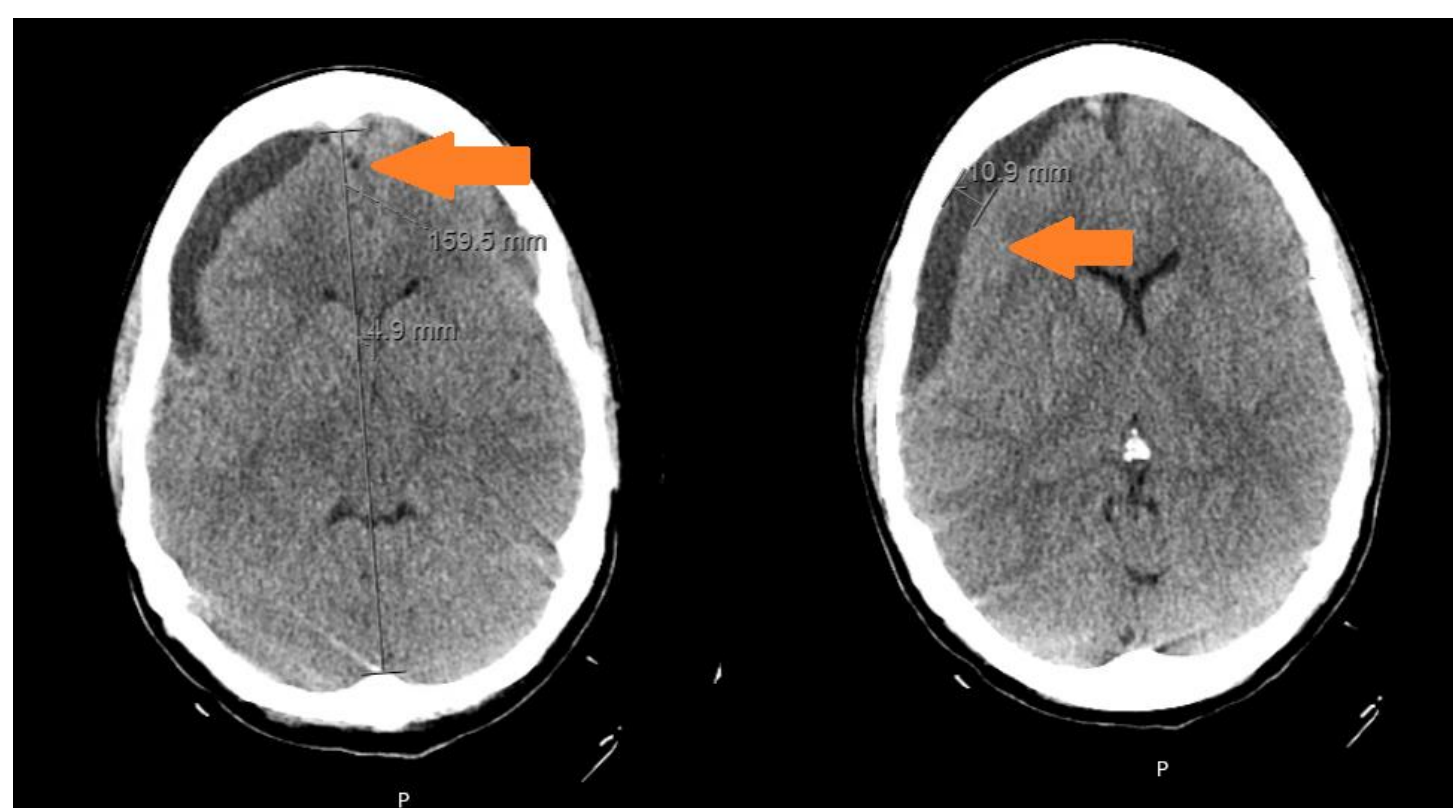


Figure 4: CT brain with (right to left) midline shift and subdural hemorrhage



The patient complained of worsening abdominal pain - CT imaging showed splenic and renal infarcts concerning for thrombosis (figure 3). Labs obtained were unequivocal for DIC (thrombocytopenia, elevated D-dimer, low fibrinogen, prolonged prothrombin time). The patient experienced associated menorrhagia, retinal hemorrhage, epistaxis, and worsening liver function. The patient additionally became unresponsive - CT head showed a new acute subdural hemorrhage and midline shift (figure 4), requiring craniotomy and evacuation. She received vitamin K. Given her liver function, gemcitabine was discontinued. Carboplatin was planned as a single agent but discontinued with worsening renal function. The patient continued to deteriorate - at the wish of family, the patient was placed on comfort measures. Shortly after, the patient was pronounced deceased approximately two months after presentation.

DISCUSSION

Thrombocytopenia in this patient was likely multifactorial - presence of an antiplatelet antibody could account for ongoing platelet count lability despite multiple platelet transfusions. However, extensive bone metastasis would also account for persistent thrombocytopenia.

Management was complicated by development of DIC. Patients with cancer are at increased risk for thromboembolic events, worsened with DIC even with thrombocytopenia - this patient was not a candidate for anticoagulation given her bleeding. DIC in solid tumors is associated with inferior survival. There is limited data to help guide appropriate treatment options in this circumstance. At this time, a combination of anti-cancer drugs, bisphosphonates, and hormone therapy as appropriate have been found to prolong survival anywhere from 12-57 months as well stabilize hematologic abnormalities, but these diseases are not curable and may not necessarily apply in the case of DIC (5-9). Future studies should identify the balance of hemotoxic chemotherapeutic regimens and acute DIC management in the hopes of further prolonging and improving the quality of life in breast cancer patients with diffuse bone marrow involvement.

TAKE-AWAY POINTS

- DIC in solid tumors is associated with inferior survival
- Anti-DIC treatments alone do not improve DIC - successful recovery involves chemotherapy

REFERENCES

1. Sallah S, Wan JY, Nguyen NP, Hanrahan LR, Sigounas G. Disseminated intravascular coagulation in solid tumors: clinical and pathologic study. *Thromb Haemost.* 2001;86(3):828-833.
2. Takeyama H, Sakiyama T, Wakasa T, et al. Disseminated carcinomatosis of the bone marrow with disseminated intravascular coagulation as the first symptom of recurrent rectal cancer successfully treated with chemotherapy: A case report and review of the literature. *Oncol Lett.* 2017;13(6):4290-4294. doi:10.3892/ol.2017.5983
3. Pasquini E, Gianni L, Aitini E, et al. Acute disseminated intravascular coagulation syndrome in cancer patients. *Oncology.* 1995;52:505-508. doi: 10.1159/000227520.
4. Kopp H, Kaus K, Fehm T, et al. Symptomatic bone marrow involvement in breast cancer - clinical presentation. *Anticancer Research.* 2011;31(11):4025-4030.
5. Freyer G, Ligneau B, Trillet-Lenoir V. Palliative hormone therapy, low-dose chemotherapy, and bisphosphonate in breast cancer patients with bone marrow involvement and pancytopenia: report of a pilot experience. *Eur J Intern Med.* 2000;11(6):329-333. doi:10.1016/s0953-6205(00)00121-7
6. Ardavanis A, Kountourakis P, Orphanos G, Rigatos G. Low-dose capecitabine in breast cancer patients with symptomatic bone marrow infiltration: a case study. *Anticancer Res.* 2008;28(1B):539-541.
7. Pahouja G, Wesolowski R, Reinbolt R, et al. Stabilization of bone marrow infiltration by metastatic breast cancer with continuous doxorubicin. *Cancer Treat Commun.* 2015;3:28-32. doi:10.1016/j.ctrc.2014.11.002
8. Bjelic-Radicic V, Stöger H, Winter R, Beham-Schmid C, Petru E. Long-term control of bone marrow carcinosis and severe thrombocytopenia with standard-dose chemotherapy in a breast cancer patient: a case report. *Anticancer Res.* 2006;26(2B):1627-1630.
9. Ishikawa T, Shimizu D, Kito A, et al. Breast cancer manifested by hematologic disorders. *J Thorac Dis.* 2012;4(6):650-654. doi:10.3978/j.issn.2072-1439.2012.10.17