Hurler syndrome and breast cancer with metastasis: A case report

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ABSTRACT

Introduction: This case report describes a patient with Hurler syndrome, which is an inherited disease commonly diagnosed within the first few years after birth. It has a series of facial characteristics, organomegaly, developmental impairments, and skeletal deformities to aid in its diagnosis, along with mutated or low levels of a-L-iduronidase, the keystone to the disease. Interestingly, without treatment, oftentimes patients will not survive for longer than school-aged years.

Case Report: The objective of this report is to discuss and explain the occurrence of breast cancer in a 32-year-old Hurler syndrome patient, who received whole body irradiation as a child as treatment for her disease. Thus far, there has been no report in the literature exploring the relationship between cancer and Hurler syndrome. This report will describe the disease, its risk factors for cancer, specifically breast cancer, current screening guidelines, prognosis, and breast cancer treatment options.

Conclusion: This case report describes the risk factors of Hurler syndrome in developing breast cancer, current screening practices, breast cancer prognosis, and treatment options. The purpose of this report is to emphasize the importance of patient-centric screening. Overall, this report adds to the literature the first known Hurler syndrome patient diagnosed with breast cancer.

Keywords: Breast cancer, Hurler syndrome, Irradiation, Metastasis

INTRODUCTION

Hurler syndrome, also known as the severe form of Type 1 mucopolysaccharidosis, is an inherited disease seen within the first years after birth, usually diagnosed by newborn screen. It is caused by a mutation defect in enzyme a-L-iduronidase, which causes inability to break down glycosaminoglycans, specifically heparin sulfate and dermatan sulfate [1]. As a result, these accumulate in lysosomes, resulting in cellular dysfunction and clinical abnormalities. Common features of Hurler syndrome include gargoyles-like facial characteristics, hepatosplenomegaly, intellectual disability, dysostosis multiplex, developmental impairment, recurrent respiratory infections, hernias, and hydrocephalus (Figure 1) [1].

Treatment depends on the severity of the disease. Attenuated disease usually requires only enzyme replacement therapy whereas the more severe form, Hurler syndrome, requires a hematopoietic stem cell transplantation (HSCT) after chemotherapy and radiation [2]. It has been shown that HSCT given to a younger patient with Hurler (likely less than two years old) can help prevent severe progression of disease, especially cognitive impairment [2]. Nevertheless, this entails having a sensitive newborn screen, keen differential diagnosis, and ability to identify the early features of disease. If left untreated, the average life expectancy for
patients with Hurler syndrome is less than eight to ten years old [1, 2].

The purpose of this case report is to understand the association between Hurler syndrome and cancer, especially breast cancer. It will discuss the screening practices needed for both Hurler patients and post-radiation treatment patients, risk factors for breast cancer, prognosis, and management for breast cancer. Thus far, there is no report in the literature that discusses Hurler syndrome and breast cancer.

CASE REPORT

In 2020, a 32-year-old female who was diagnosed with Hurler syndrome at one year of age presented with a left upper outer quadrant breast mass that she noticed during a shower. At the time, she denied breast pain, nipple discharge, and weight loss. At 30 months old, this patient underwent an open liver biopsy and a bone marrow aspirate, which were consistent with mucopolysaccharidosis. At 31 months old, our patient had 1200 cGy of whole-body irradiation and concurrent chemotherapy as a conditioning regimen prior to bone marrow transplantation with good response. She also had a left sided ventriculoperitoneal shunt placed for hydrocephalus around the same time. She has been receiving Depo-Provera injections for dysmenorrhea since adolescence and a previous attempt to remove her uterus and ovaries failed due to excessive intra-abdominal adhesions. This patient’s risk factors for breast cancer include previous radiation, nulliparity, obesity, and hormonal therapy (progestin). She has never had a previous breast biopsy and does not have a family history of ovarian or breast cancer.

On clinical examination, a 6 × 5 cm firm, irregular, nonmobile mass with slight skin hyperpigmentation at the retro-areolar area extending to the axillary tail of the left breast was found. There was no nipple retraction or palpable or matted axillary lymph nodes. Work-up was conducted and mammogram on July 2020 showed two adjacent spiculated masses or one multi-lobulated spiculated mass with an overall size of 3.4 × 1.7 cm on the left breast 12 to 1 o’clock anterior depth, where there was a palpable lump (Figure 2A). Smaller nodular densities were projected along the posterior margin of this lesion and a separate 6 mm nodule noted at the 11:30 position posterior depth was also found (Figure 2B). A left breast ultrasound showed a large multi-lobulated hypoechogenic solid mass with internal blood flow measuring 3.2 × 1.6 × 1.7 cm at 1 o’clock 2 cm from the nipple and an 8 × 6 mm solid nodule at 1 o’clock (Figure 3A and B). Left axilla showed an abnormal-appearing lymph node measuring 2.2 × 1.2 × 2.1 cm in size with a markedly thickened cortical mantle measuring 9 mm (Figure 3C). Ultrasound guided left breast and left axillary core needle biopsy were performed and pathology showed invasive ductal carcinoma, grade 2, ER+ PR+ HER2 negative (pathology report below). Staging computed tomography (CT) of the chest, abdomen, and pelvis showed the left breast and axillary mass (Figure 4A), a liver mass (Figure 4B), a left adrenal nodule (Figure 4C), and numerous lung lesions, concerning metastatic disease. In addition, a bone scan showed a focus of increased uptake within the left mid-femoral diaphysis that may represent metastatic focus (Figure 5). Nevertheless, the positron emission tomography (PET) scan showed a 2.9 cm lobulated left breast mass and 12.5 left axillary node with hypermetabolic activity (Figure 6A and B), innumerable bilateral lung nodules without hypermetabolic activity (Figure 6C), and a 1.3 cm left adrenal nodule with minimal hypermetabolic activity (Figure 6D). No other hypermetabolic foci are identified in the neck, chest, abdomen, and pelvis as well as no skeletal hypermetabolic activity. Based on the current American Joint Committee on Cancer (AJCC) TNM staging, our patient’s clinical stage is T2N1M1: Stage 4 [3]. Her treatment for metastatic breast cancer includes an aromatase inhibitor, CDK4/6 inhibitor, and ovarian suppression. As far as follow-up, the patient is being followed by our oncology team and a future repeat staging study will be done to assess her response to treatment. She is also being followed by our breast surgery team for clinical exam follow-up.

Figure 1: Characteristics of Hurler syndrome.
Figure 2: (A) Left breast mammogram mediolateral oblique view (MLO) shows a $3.4 \times 1.7$ cm multilobulated spiculated mass at 12 to 1 o’clock anterior depth. Smaller nodular densities were projected along the posterior margin of this lesion. (B) Left breast mammogram craniocaudal view (CC) shows a separate 6 mm nodule noted at the 11:30 position posterior depth.

Figure 3: (A) Ultrasound of the left breast shows a large $3.2 \times 1.6 \times 1.7$ cm multilobulated hypoechoic solid mass with internal blood flow, at 1:00 position 2 cm from the nipple in the region of the palpable lump. (B) Ultrasound of the left breast shows an $8 \times 6$ mm solid nodule at 1:00 position corresponding to the small solid nodule on mammogram. (C) Ultrasound of the left axilla shows an abnormal-appearing lymph node measuring $2.2 \times 1.2 \times 2.1$ cm in size with a markedly thickened cortical mantle measuring 9 mm.

Figure 4: CT chest, abdomen, and pelvis show a left breast mass and a VP shunt that is seen running through the left abdominal and chest wall (A), a liver mass (B), and a left adrenal nodule (C).

Figure 5: Nuclear medicine bone scan shows a focus of increased uptake within the left mid femoral diaphysis that may represent metastatic focus.

Figure 6: PET scan with CT skull to thigh shows a 2.9 cm lobulated left breast mass and 12.5 left axillary node with hypermetabolic activity (A and B). Innumerable bilateral lung nodules without hypermetabolic activity (C). 1.3 cm left adrenal nodule with minimal hypermetabolic activity (D).
Pathology Report for Left Breast and Left Axilla Biopsy

1. Left Breast, 1:00, Biopsy

INVASIVE DUCTAL CARCINOMA

Comment: The biopsy shows invasive ductal carcinoma, Nottingham grade 2 of 3 (tubule formation-3, nuclear pleomorphism-3, mitotic count-1). The tumor involves multiple cores and measures at least 1 mm in greatest contiguous dimension.

2. Left Axilla, Biopsy

INVASIVE DUCTAL CARCINOMA IN A BACKGROUND OF FIBROSIS

Estrogen Receptor (SP1): Positive (> 95% strong positive)
Progesterone Receptor (1E2): Positive (80% moderate positive)
Her2/neu (4B5): Negative

DISCUSSION

A. Risk Factors and Screening Practices

Breast cancer is the most common female cancer in the United States, and second to lung cancer globally; it is also one of the leading causes of cancer death in the United States and worldwide [4]. Non-modifiable risk factors for breast cancer include genetic predisposition, race, with breast cancer incidence being higher among Caucasian women [5], increased duration of lifelong estrogen exposure due to early menarche, late menopause, and/or nulliparity [6], dense breast tissue, and previous exposure to radiation [7–10].

As stated, exposure to ionizing radiation of the chest at a young age is a major risk factor for breast cancer, such as atomic bomb, nuclear plant accident survivors, patients with Hodgkin lymphoma, and alike, in our patient discussed above who had radiation as part of treatment for Hurler syndrome. A source suggests that the most vulnerable age for exposure to radiation is between 10 and 14 years old [10]. Modifiable risk factors for breast cancer include obesity, use of hormonal therapy, alcohol use, environmental exposure, and smoking [7]. Protective factors include physical activity, breastfeeding, and diet modification [7]. While alcohol use has been associated with increased risk of breast cancer, studies on other dietary factors such as increasing fruits, vegetables, and decreasing fat/red meat consumption have been mixed [7].

Our literature search did not reveal specific cancer risk linked to Hurler syndrome alone. However, secondary malignancy due to childhood radiation, chemotherapy [9, 11], and hematopoietic stem cell transplant [12], have been described and may have played a role.

A woman is considered high risk for breast cancer if she had radiation treatment to the chest area between ages 10 and 30 [8]. According to National Comprehensive Cancer Network (NCCN) guidelines, a patient with a history of radiation treatment to the chest area between ages 10 and 30 is considered high risk and screening should start 10 years after radiation treatment, including a clinical breast exam every year for patients under 25 years old; clinical breast exams every 6–12 months for patients 25–29 years old, plus yearly mammogram and magnetic resonance imaging (MRI) for patients age 30–75 [8]. Otherwise, yearly screening mammograms are recommended starting at age 40 for the average risk women.

B. Treatment Management for Breast Cancer

Treatment for breast cancer depends on tumor size and type, status of tumor markers, presence of metastatic disease, genetic testing results when indicated, and most importantly, a patient’s preference and goal.

The patient discussed above has a hormone positive invasive ductal carcinoma, which is the most common type of invasive breast cancer [4]. In the absence of metastatic disease, treatment would typically include locoregional control of the tumor, which includes either a lumpectomy or postoperative radiation versus a mastectomy and surgical axillary staging, followed by endocrine therapy [3]. Chemotherapy administration would depend on tumor recurrence score and the presence of metastasis in the axillary lymph node [3]. However, in the setting of metastatic disease, such as in our premenopausal patient, treatment includes an aromatase inhibitor, CDK4/6 inhibitor, and ovarian suppression [3].

Metastatic disease monitoring includes periodic assessment with serial physical examinations, laboratory tests including biomarkers if indicated, and imaging studies. Determination needs to be made regarding whether the disease is controlled and whether treatment toxicity is acceptable [3]. In the end, a shared decision-making process with patients and family is crucial and dictates the treatment pathway.

C. Prognosis for Breast Cancer

While the 5-year survival rate for early stage breast cancer (I–II) is 99%, the 5-year survival rate for breast cancer with distant metastasis (Stage IV) is 27% [13]. The median overall survival of metastatic breast cancer is about two years [13]. However, this can range from months to many years.

Moreover, clinical prognostic factors affect survival. Patients with chest wall, bone, or nodal metastasis may have prolonged progression free survival compared to those with hepatic and/or pulmonary disease [14]. Hormone positive disease has a more favorable prognosis compared to triple negative or HER2 positive disease [14]. Negative prognostic factors include poor performance status, weight loss, and age less than 35 years old [14].
Gene expression analyses such as the Oncotype Dx-21 gene recurrence score has been shown to be a useful prognostic tool for survival [15, 16].

D. Status-Post Irradiation-linked Cancers

Given the management Hurler patients receive, they are placed at an increased risk of several other cancers not discussed above. More specifically, Hurler patients undergo whole body radiation and myeloablative chemotherapy prior to hematopoietic stem cell transplants. It has been noted that among 4905 patients who underwent radiation and transplantation (for other causes besides Hurler syndrome), “a 22% cumulative incidence of subsequent malignant neoplasms by 30 years after transplantation [occurred] [12].” In other words, “compared with age, sex, calendar year-matched Surveillance, Epidemiology, and End Results population rates, the standardized incidence ratio of subsequent malignant neoplasms was increased 2.8-fold [12].” The most likely cancer development was found in bone, the oral cavity, skin, central nervous system, and endocrine organs with the highest excess absolute risk seen in breast cancer, skin, and the oral cavity [12].

It was also noted that there was a positive correlation between radiation dose and fractionation with risk of malignancy, being that higher-dose radiation fractionated (1400–1750 cGy) and unfractionated (600–1000 cGy) radiation had higher incidence, specifically eight times higher than normal [12]. The lower-dose radiation (200–450 cGy) incidence was comparable to chemotherapy incidence, which is still two times higher than normal [12]. This can likely be attributed to the cytotoxic damage that radiation, especially higher dosing, induces on normally dividing cells, solidifying increased risk of cancer growth in those areas. Other risk factors that increase a patient’s risk of subsequent malignancy following a hematopoietic stem cell transplant is white race and younger age at transplant (less than 20 years old) [12]. Thus, healthcare for those who undergo whole body irradiation, and even chemotherapy, should place significant importance on early screening, detection, and education on its long-term effects.

CONCLUSION

This case report highlights the importance of understanding Hurler syndrome risk factors in developing breast cancer and despite current guidelines, the importance of patient-centered screening practices. It also solidifies breast cancer prognosis and management, emphasizing the importance of early screening and diagnosis. With Hurler syndrome management commonly being whole body radiation, chemotherapy, and eventual hematopoietic stem cell transplantation, many patients live longer than previously noted; this constitutes a larger incentive for earlier patient-centered cancer screening and education on long-term risk factors.

REFERENCES


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Author Contributions
Avalon Regalbuto – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Eveline Klenotic – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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