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Cervical Cancer at A Young Age: Considering Fanconi Anemia as Part of the Clinical Workup

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Abstract

Background: Fanconi Anemia (FA) is a rare inherited autosomal recessive disorder that carries an increased risk of leukemia, squamous cell carcinoma of the head, neck and cervix due to homozygous mutations in FA genes leading to defective DNA repair. These same mutations when heterozygous may be associated with cancer, intrinsic chemotherapy resistance (FANCD2) and hypersensitivity (FANCA).

Case: A 22-year-old woman with a history of anemia presented with rapid progression of cervical dysplasia to squamous cell carcinoma of the cervix. She developed aplastic anemia during chemo-radiation and was subsequently diagnosed with Fanconi anemia.

Conclusion: Rare conditions such as Fanconi Anemia should be considered when the clinical course varies significantly from the norm. Consultations with hematology and genetic services may elucidate other possible contributing factors.

Keywords: Cervical cancer; Fanconi anemia; Human papilloma virus

Introduction

The median age of cervical cancer diagnosis is 49, with an incidence of 7.5 per 100,000 women per year [1,2]. Of patients with new diagnoses, 14.0% are 34 years old or younger, and less than 0.1% are younger than 20 years of age [2]. HIV is one of the most significant risk factors for early development of cervical cancer due to its impact on the immune system, and all women diagnosed with cervical cancer should undergo HIV testing. On average, seropositive individuals are diagnosed with cervical cancer 10 years earlier than those who are seronegative [3]. One additional diagnosis to consider in a patient diagnosed at an age considerably younger than the mean is Fanconi Anemia (FA). FA carries an increased risk of squamous cell carcinoma of the head, neck, and cervix, as well as leukemia due to mutations in DNA repair pathways [4]. These same mutations may also be associated with intrinsic treatment resistance (overexpression of FANCD2 protein) and hypersensitivity (FANCA), including to DNA cross-linking agents such as cisplatin [5]. This disease is most often autosomal recessive but can be X-linked, and genetic testing in family members may be indicated [6].

For women with FA who develop cervical cancer, cisplatin given during chemoradiation can produce a profound response [4]. There are currently no standard guidelines for treating these individuals' cancer. In one reported case, a patient with FANCA heterozygosity developed pancytopenia and protracted thrombocytopenia requiring transfusion, as well as anemia, alopecia, diarrhea and nausea causing a 2-week interruption in her treatment for cervical adenocarcinoma [7]. That patient completed radiation without cisplatin therapy, and had residual tumor. She went on to have a hysterectomy with multiple subsequent postoperative complications. The case we present here demonstrates the clinical clues that, in hindsight, should have raised suspicion of FA in a young woman with cervical cancer, and reviews the treatment course that ultimately led to her diagnosis.

Case

The patient is a 22-year-old G0 with a family history

significant for a mother with cervical cancer and a father with squamous cell carcinoma of the head and neck. The patient's past medical history is significant for a ventricular septal defect that did not require surgical repair. She had multiple workups for anemia as early as age 13 with no definitive cause identified. Despite national Pap smear guidelines recommending initiation of cervical cancer screening at age 21, she started having pap smears at age 17 due to her family history. Her first pap was Low-Grade Squamous Intraepithelial Lesion (LSIL), HPV negative. One year later, following an ASCUS HPV positive Pap smear, she had CIN1 on colposcopic biopsy, with a benign endocervical curettage. She completed a 3-dose series of the quadrivalent HPV vaccine at age 20, after the initiation of sexual activity and after her first abnormal pap smear.

Two years later, she had her first High-Grade Squamous Intraepithelial Lesion (HSIL) Pap smear at the age of 22 with subsequent colposcopic biopsy demonstrating squamous cell carcinoma. Visual inspection revealed a diffusely friable cervix without an obvious lesion. HIV testing was negative. She had a PET CT demonstrating avidity at cervix only. She underwent a Cold Knife Cone Biopsy (CKC) measuring 3.0x2.6x2.4 cm with positive Lympho-Vascular Space Invasion (LVSI), endocervical and ectocervical margins positive for invasive carcinoma, with 6 mm depth of invasion and positive horizontal margins. Based on her CKC and physical exam, she was diagnosed with Stage IB1 cervical cancer. Treatment recommendations from the National Comprehensive Cancer Network (NCCN) for stage IB1 cervical cancer includes either radical hysterectomy with lymph node dissection or with External Beam Radiation Therapy (EBRT) +/- cisplatin chemotherapy [8]. Her tumor met Sedlis criteria for adjuvant radiation following surgery so the decision was made to proceed directly to definitive chemoradiation [8]. The patient underwent an oncofertility consultation, oocyte retrieval, and laparoscopic ovarian transposition. She developed a small bowel obstruction 17 days later and underwent an exploratory laparotomy with excision and reanastomosis of strangulated bowel incarcerated in one of the sutures from the ovarian transposition.

The patient's Complete Blood Count (CBC) at the time of her CKC was WBC of 2.75 K/cu mm, ANC 1.1 k/cu mm, platelets of 151 k/cu mm and hemoglobin 10.4 g/dL. She developed significant myelosuppression after completion of one cycle of cisplatin with her radiation treatment. She went on to develop aplastic anemia confirmed by bone marrow biopsy on two separate occasions. Secondary malignancy such as leukemia was ruled out. She received transfusions of packed red blood cells and platelets with an appropriate rise initially. However, pancytopenia persisted and chemoradiation was no longer a viable treatment option. The case was discussed at the multidisciplinary tumor board and surgical resection was recommended. She underwent a robotic assisted radical hysterectomy with bilateral pelvic lymph node dissection. Final surgical pathology found no residual dysplasia or malignancy in the uterus, cervix or lymph nodes. Hematology was consulted postoperatively for persistent pancytopenia. Her history of anemia, combined with her hematologic abnormalities prior to treatment and aplastic anemia in response to chemoradiation suggested a genetic bone marrow failure syndrome.

The patient underwent additional workup with Hematology and Genetic Counseling. Chromosome breakage testing showed shortened telomeres consistent with Fanconi Anemia. Genetic testing revealed two mutations in FANCA, c.11C>A (p.Ser4Ter) which is pathogenic, and another mutation, likely pathogenic c.3391A>G (p.Thr1131AIa). At that time her blood counts had improved and bone marrow transplant was not recommended. She was started on Danazol for treatment of bone marrow failure [9]. Genetic testing was recommended for her parents and sister.

This patient is now undergoing surveillance for myelodysplastic syndrome and acute leukemia by bone marrow biopsy 1-2 times a year. She has not received any further chemoradiation therapy. Despite ovarian transposition the patient has developed hypoestrogenic symptoms and has subsequently been started on hormone replacement therapy.

Discussion

FA often presents with short stature, abnormal skin pigmentation, skeletal malformations (radial aplasia) of the upper and lower limbs, microcephaly, and ophthalmic and genitourinary tract anomalies [1]. It can also present as pancytopenia or bone marrow failure in individuals without this phenotype; often showing early signs within the first decade and slowly progressing [2]. These can often be subtle.

The pathophysiology of cervical cancer in FA is unclear but it is thought that FA alters an individual's ability to repair cellular changes associated with HPV acquisition, a key step in the development of cervical dysplasia and cancer. HPV oncogenes E6 and E7 are responsible for initiating the transition towards malignancy. E6 does so by inactivating p53, a tumor suppressor gene. E7 binds the pRB tumor suppressor protein which causes subsequent degradation [10]. Individuals with FA have impaired damage repair mechanisms for DNA cross-links and double-strand breaks [5,11]. This leads to accumulation of mutations that cause genomic instability and increased risk of developing cancer [12].

The National Cancer Institute Bone Marrow Failure (BMF) Syndrome Cohort include more than 500 patients with the 4 BMF syndromes and cancer, with FA being the largest group [13]. The rate of cancer development is highest in FA out of all 4 major bone marrow failure syndromes with the most frequent genotypes in patients with cancer in the cohort were FANCA and FANCC. However, there was no association of genotype with cancer type: in 70 patients (men and women) with FANCA mutation there were

11 cancers, while 3 of 19 patients with FANCC mutation found to have cancer [13]. Yet, carcinoma of the cervix was not found in this cohort of FA patients. The degree of anemia if profound in FA patients even after bone marrow transplant.

Research has shown that individuals with FA have an appropriate immune response to the HPV vaccine and will likely benefit from completion of the vaccine series prior to onset of sexual activity [14]. Limited research does not show an increased risk of cervical cancer in individuals who are heterozygous for a FA gene mutation, though there may be an association with heightened sensitivity to chemotherapy and radiation therapy seen in homozygotes [7].

This case highlights the importance of considering additional diagnoses and involving a multidisciplinary team when caring for a patient whose clinical course does not fit the typical presentation. This young woman had a history of anemia of unknown cause, with low white cell counts and platelets prior to any treatment, as well as abnormal pap smears starting with her first one at age 17. She received the HPV vaccine but likely did not receive the full benefit, as it was not given prior to coitarche. Universal vaccination for children is imperative in order to fully realize the potential for primary prevention of HPV related cancers. FA is a rare disease that can have a significant impact on the clinical treatment course of an individual diagnosed with cervical cancer, and should be considered in a young woman with cervical cancer especially in the setting of hematologic abnormalities or other phenotypic features consistent with the disease. Following diagnosis, individuals with FA need ongoing surveillance by gynecologic oncology and with hematology and primary care to ensure they do not develop other associated diseases. Ongoing work promoting HPV vaccination, identification of individuals who may have a genetic component to their disease process, and multidisciplinary treatment and surveillance collaboration are imperative.

Conclusion

Women with FA may not have any distinguishable phenotypic features. Exposure to stress of cytotoxic treatment may reveal the diagnosis of FA, as shown in this young woman with cervical cancer. The recognition of the syndrome was essential for the improvement in treatment choice and the patient was treated with radical surgery.

Author's contributions

All listed authors made substantial contributions to the creation, revision, and approval of this manuscript.

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