

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

Greta Weaver, Amanda Bruegl, Tanja Pejovic* and Melissa Moffitt

Department of Gynecologic Oncology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA

Abstract

Background: Fanconi Anemia is a rare condition that carries an increased risk of squamous cell carcinoma of the head, neck and cervix due to mutations in DNA repair pathways. These same mutations may also be associated with intrinsic treatment resistance (FANCD2) and hypersensitivity (FANCA).

Case: A 22-year-old woman with a history of anemia who presented with rapid progression to squamous cell carcinoma of the cervix. She developed aplastic anemia during chemoradiation 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 genetics may elucidate other possible contributing factors. HPV vaccination remains an underutilized method for primary prevention of cervical cancer and should be promoted among eligible populations.

Publication History:

Received: June 11, 2018

Accepted: August 02, 2018

Published: August 04, 2018

Keywords:

Fanconi anemia, Cervical cancer, Human papilloma virus, Colposcopic biopsy, Genetic testing

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 those new diagnoses, 14.0% are 34 years old or younger, and less than 0.1% are below 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 as such 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. It 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 (FANCD2) 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 individuals with Fanconi Anemia 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. One case reported a patient with FANCA heterozygosity who developed pancytopenia and protracted thrombocytopenia requiring transfusion, as well as anemia, alopecia, diarrhea and nausea which caused 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 following case demonstrates the clinical clues that, in hindsight, should have raised suspicion of Fanconi Anemia 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 Girl 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 LSIL, HPV negative. One year later, following an ASCUS HPV positive pap, 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 HSIL pap 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 lymphovascular space invasion (LVSI), endocervical and ectocervical margins positive for invasive carcinoma, with 6mm 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

Corresponding Author: Dr. Tanja Pejovic, Department of Gynecologic Oncology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239-3098, USA, Tel: 503-418-9382, Fax: 503-418-4048; E-mail: pejovict@ohsu.edu

Citation: Weaver G, Bruegl A, Pejovic T, Moffitt M (2018) Cervical Cancer at a Young Age: Considering Fanconi Anemia as Part of the Clinical Workup. Int J Gynecol Clin Pract 5: 139. <https://doi.org/10.15344/2394-4986/2017/139>

Copyright: © 2018 Pejovic et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

small bowel obstruction 17 day 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 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 on 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. Her 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. 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. She underwent evaluation for possible infectious etiology as well as bone marrow biopsy and genetic testing. Final surgical pathology found no residual dysplasia or malignancy in the uterus, cervix or lymph nodes.

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 which is likely pathogenic c.3391A>G (p.Thr1131Aa). She does not have a family history of Fanconi Anemia. 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

Fanconi Anemia 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.

Fanconi Anemia 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].

Research has shown that individuals with Fanconi Anemia (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 [13]. Even if a person is already infected with HPV they can still benefit from vaccination against other strains of the virus [14]. Limited research does not show an increased risk of cervical cancer in individuals who are heterozygous for a Fanconi gene mutation, though there may be an association with heightened sensitivity to chemotherapy and radiation therapy seen in homozygotes [7].

The current CDC recommendations for HPV vaccination (available in their entirety at <https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html>) are as follows:

1. Routine vaccination at age 11-12, but can start as early as 9. Two doses 6-12 months apart. If less than 5 months apart, give a third dose.
2. Completion of incomplete vaccination for females age 13-26, males age 13-21, and through age 26 for males who are sexually active with other men, transgender, or immunocompromised (including but not limited to HIV infection).
3. Give 3 doses if vaccination started after age 15 or if immunocompromised. Vaccine is to be given at 0, 1-2, and 6 months [14].

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. Fanconi Anemia 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 Fanconi Anemia 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.

Competing Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author's Contributions

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

References

1. Cancer of the Cervix Uteri - Cancer Stat Facts.
2. Young N (2012) Aplastic anemia, Myelodysplasia and related bone marrow failure syndromes. In: Longo DL, ed. *Harrison's Principles of International Medicine* 1: 887.
3. Ntekim A, Campbell O, Rothenbacher D (2015) Optimal management of cervical cancer in HIV-positive patients: a systematic review. *Cancer Med* 4: 1381-1393.

-
4. Mathew CG (2006) Fanconi anaemia genes and susceptibility to cancer. *Oncogene* 25: 5875-5884.
 5. Kim H, D'Andrea AD (2012) Regulation of DNA cross-link repair by the Fanconi anemia/BRCA pathway. *Genes Dev* 26: 1393-1408.
 6. Reference GH (2017) Fanconi anemia. *Genetics Home Reference*.
 7. Sirák I, Šinkorová Z, Šenkeříková M, Špaček J, Laco J, et al. (2015) Hypersensitivity to chemoradiation in FANCA carrier with cervical carcinoma-A case report and review of the literature. *Rep Pract Oncol Radiother* 20: 309-315.
 8. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer.
 9. Townsley DM, Dumitriu B, Liu D (2016) Danazol Treatment for Telomere Diseases. *N Engl J Med* 374: 1922-1931.
 10. Gao G, Smith DI (2017) Human Papillomavirus and the Development of Different Cancers. *Cytogenet Genome Res* 150: 185-193.
 11. Kee Y, D'Andrea AD (2012) Molecular pathogenesis and clinical management of Fanconi anemia. *J Clin Invest* 122: 3799-3806.
 12. Park S, Park JW, Pitot HC, Lambert PF (2016) Loss of Dependence on Continued Expression of the Human Papillomavirus 16 E7 Oncogene in Cervical Cancers and Precancerous Lesions Arising in Fanconi Anemia Pathway-Deficient Mice. *MBio* 7: 00628.
 13. Alter BP, Giri N, Pan Y, Savage SA, Pinto LA, et al. (2014) Antibody response to human papillomavirus vaccine in subjects with inherited bone marrow failure syndromes. *Vaccine* 32: 1169-1173.
 14. HPV Vaccine Recommendations (2017) Human Papillomavirus. CDC.