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Causes and Palliation of Transfusion-Associated Vaginal Bleeding in Patients with Metastatic Cancer

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Abstract

PURPOSE—The current study was undertaken 1) to capture a clinically relevant, systematically-collected series of patients with metastatic cancer and transfusion-associated vaginal bleeding and 2) to provide insight into how best to palliate this bleeding.

METHODS/RESULTS—As part of a single-institution review, 46 patients with metastatic cancer and transfusion-associated vaginal bleeding were identified. In a minority, 14 (30%), the cancer itself was directly responsible for the bleeding, and, under these circumstances, a gynecological cancer was the most frequent cause. In 13 patients (28%), more than one palliative intervention was attempted. Of all the interventions, a hysterectomy was used most frequently and was successful in 11 patients. The use of ablation or embolization procedures was rarely tried but successful in 4 patients. However, 2 patients died from the vaginal bleeding, despite multiple palliative procedures to control bleeding, including tumor embolization in one.

CONCLUSIONS—Transfusion-associated vaginal bleeding in patients with metastatic cancer can arise from non-malignant causes, often assumes an uneventful course, but can, at times, be serious and difficult to control.

Keywords

vaginal bleeding; uterine bleeding; palliation; hemorrhage; anemia

Park and others described a 28 year-old-woman who presented with “massive vaginal bleeding and anemia”[1]. After biopsy-confirmation of a recurrent alveolar soft part sarcoma diagnosed 6 years earlier, this patient went on to receive 6 Gy of vaginal radiation, which controlled her bleeding. Indeed, the published medical literature is peppered with similar cases or case series of vaginal bleeding in cancer patients who have required a spectrum of invasive, targeted, and otherwise infrequently-used palliative interventions. These include radiation, surgery, uterine artery embolization or ligation, balloon tamponade, vaginal packing, or unusual topical interventions, such as Mohs paste, cisplatin, or acetone [2–16]. This literature also suggests that in patients with major bleeding or with a concurrent bleeding diathesis, blood product support, antifibrinolytics, or vitamin K can be used. Aptly, this literature describes how patients can die from this cancer-related complication but how the interventions mentioned above can be life-saving.

Are such interventions necessary for the majority of cancer patients who develop transfusion-associated vaginal bleeding? Based on the totality of published reports, the

implication is that patients with metastatic cancer and transfusion-associated vaginal bleeding often must rely on such invasive, heroic interventions for palliation. To some clinicians, it may remain unclear whether these published palliative interventions are representative of current practice or whether they illustrate a predilection to publish only the more aggressive and successful reports.

Hence, the current study was undertaken with a twofold purpose. First, it sought to capture a clinically relevant, systematically-collected series of patients with metastatic cancer and vaginal bleeding with the goal of capturing a more inclusive array of management approaches and outcomes. It was thought that such a systematic approach might provide a more grounded perspective on current practice. Second, it sought to provide healthcare providers with a higher level of evidence-based insight on how best to manage patients with metastatic cancer and transfusion-associated vaginal bleeding.

METHODS

Overview

The Mayo Clinic Institutional Review Board approved this study, which utilized the medical records of cancer patients seen at the Mayo Clinic in Rochester, Minnesota from 1998 to the beginning of 2013. The 1998 start-year was chosen because it coincides with the more general use of diagnostic tests, namely, vaginal ultrasound, that better characterize the etiology of vaginal bleeding [17,18].

The study team used a data retrieval specialist from the Division of Biomedical Statistics and Informatics to acquire a list of patients who had concurrent diagnoses of metastatic cancer and abnormal vaginal bleeding; this person's sole role is to assist in data set retrieval for research purposes. International Classification of Disease (ICD) codes 626.4, 626.6, 626.8, and 626.9 were used initially to identify patients, as per the International Classification of Diseases, 9th Revision, Clinical Modification, 2012. The term metastatic cancer was defined as a malignancy that had spread outside the primary organ of origin, and abnormal vaginal bleeding was defined as bleeding that was inconsistent with normal menstruation. Patients undergoing bone marrow transplantation with normal menstruation were excluded. In an effort to focus this study on patients with severe bleeding, patients also had to have received a transfusion of packed red blood cells.

Medical Record Review

Initial medical record data extraction was undertaken by one author (EKS); the other two authors (AEJ and AJ) independently re-reviewed portions of each medical record to confirm accuracy. The following information was extracted from each patient's medical record: dates of birth, cancer diagnosis, first episode of vaginal bleeding, blood transfusion, and death or last follow up; types of cancer treatment administered; interventions to palliate bleeding; success of each intervention over the ensuing 3 months; and whether bleeding later recurred. Information on the comorbidities of coronary artery disease and bleeding diathesis above and beyond that conferred by cancer were also extracted from each record. The 3-month interval, referred to above, was chosen because of its precedent in defining the success of interventions in other cancer settings [5,19,20]. The decision to seek information on the morbidities of coronary artery disease and bleeding diathesis were based on a high likelihood of lowering the thresholds of transfusion and bleeding, respectively. Finally, overall survival, as calculated from the time of vaginal bleeding to death, was also reported.

Data Analyses

This study was intended to be descriptive in nature. Data were organized with JMP™ 9.0.1, SAS® Institute Inc, Cary, North Carolina, USA. If a specific date was unavailable in the medical record, a mid-interval date was imputed as an approximation. Data are presented as frequencies, percentages, and medians with ranges.

RESULTS

Demographics

Only 46 met this study's eligibility criteria. This group of patients was culled from much larger groups that included 242 patients with metastatic cancer and vaginal bleeding and that included 2941 women diagnosed with metastatic cancer at the Mayo Clinic during this same period.

The median age of the patients in this study was 45 years (range: 15, 74). The most frequently observed cancer type within the cohort was breast cancer, which was observed in 13 patients (25%). Four patients had ischemic heart disease, and 5 had a bleeding diathesis. Other demographic data appear in Table 1.

Etiology of Abnormal Vaginal/Uterine Bleeding

Interestingly, in only a minority of patients, 14 (30%), cancer metastases or direct extension of the primary tumor was responsible for the vaginal bleeding (Table 2). Most commonly, the etiology of the bleeding was unclear or unknown. In instances where the cancer itself was the cause, gynecological cancers were the most culpable, but other malignancies were also implicated. The need for blood transfusions could not always be directly attributed to the vaginal bleeding and appeared at times to be used to correct a multifactorial anemia.

Interventions and Outcomes for Abnormal Vaginal/Uterine Bleeding

In 13 patients (28%), more than one intervention was attempted to palliate the vaginal bleeding. Of all the interventions employed, a hysterectomy was used most frequently and appeared successful in 11 patients (Table 3). Ablation or embolization procedures were rarely undertaken but were successful in all but one patient.

At the time of this report, 25 patients (53%) are deceased. The median survival following vaginal bleeding was 2.2 years. Two patients died from the vaginal bleeding. These patients had renal and endometrial cancer, respectively, and underwent multiple palliative procedures performed in an effort to control bleeding, including tumor embolization in one.

DISCUSSION

In contrast to previous reports, most patients with metastatic cancer and vaginal bleeding in this series manifested a benign course [1–16]. In fact, in the majority of patients, the bleeding was not directly related to cancer localization, either primary or metastatic to the genital tract. Hormonal therapy was often a cause of bleeding, and these patients were often palliated with hormonal manipulation or dilation and curettage. When the cancer was the direct cause, a gynecological cancer was often the culprit, and these patients' bleeding was often palliated by means of a hysterectomy.

Despite an often-benign course, a few patients, namely, two, died from bleeding. Although published case reports often appear to describe the most favorable outcomes from invasive palliative interventions, this systematic case series observed that some patients, who had invasive palliative procedures -- such as embolization and radiation -- did not derive benefit

[1–16]. Thus, the current report provides important perspectives to healthcare providers as they counsel cancer patients under such dire circumstances of hemorrhage: invasive interventions can provide palliation -- but sometimes they do not. Cancer patients who have widespread metastases and who are confronted with the options of invasive, non-curative interventions should thus be counseled that such approaches can, at times, be ineffective.

This study has strengths and weaknesses. In terms of the latter, a major challenge of any retrospective study is the inherent bias related to patient and treatment selection. Indeed, it is difficult to assess treatment outcomes in a definitive manner in this setting, as the more severely ill patients likely received the more aggressive interventions. With transfusion-associated vaginal bleeding, however, it is unlikely that a prospective trial will be conducted in the near future, and, hence, the experience reported here is of value. A major strength of this study is its achievement of providing balance to the published literature; this study captures both favorable and unfavorable outcomes. Importantly, this study provides a relatively robust clinical experience on an understudied topic that directly impacts a small subgroup of women with metastatic cancer. Next steps might include reviewing the management of vaginal bleeding in patients with metastatic cancer within a larger, multi-institutional group of patients.

In summary, transfusion-associated vaginal bleeding in patients with metastatic cancer often occurs from non-malignant causes, sometimes assumes an uneventful course, and sometimes can be managed with relatively non-invasive approaches. For the times when bleeding appears more serious and difficult to control, invasive strategies can be helpful but are not always. Hence, patients with widespread metastatic cancer and serious bleeding should be counseled in a balanced manner.

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Table 1

Type of Primary Cancer (n=46)*

Cancer Type	Number of Patients	Percentage of Patients
Breast	13	28
Gynecological	8	17
Gastrointestinal	6	13
Genitourinary	3	7
Hematologic	3	7
Other*	13	28

* This category includes 4 patients with primary adrenal cancer, 2 with lung cancer, and one each with parotid cancer, a synovial sarcoma, melanoma, head and neck cancer, and a central nervous system malignancy.

Table 2

Cancer Treatment Modality (n=46)*

Cancer Treatment	Number of Patients	Percentage of Patients
Surgery	40	85
Radiation	33	70
Chemotherapy	39	83
Hormonal therapy	14	30
Other	10	21

** Numbers of patients do not sum to 46 and percentages do not sum to 100% because patients often received more than one type of treatment.

Table 3

Etiology of Vaginal Bleeding

CATEGORY	NUMBER OF PATIENTS	PERCENTAGE OF PATIENTS
Primary Cancer Type	14	30
Uterine corpus	6	
Uterine cervix	2	
esophagogastric	1	
renal	1	
bladder	1	
melanoma	1	
hematologic *	1	
lung	1	
Hormonal therapy/tamoxifen	6	13
Non-malignant uterine pathology	10	22
Unknown/unclear	16	35

* This patient with a hematologic malignancy also had metastatic breast cancer, but the former was listed here, as it was the more recent cancer diagnosis.

Table 4**Interventions for Vaginal Bleeding***

Intervention	Did it work? (no bleeding for 3 months)		
	Yes	No	Not Sure
hormonal manipulation/Mirena intrauterine device (IUD)	7 (16)	4 (9)	--
dilatation and curettage	7 (15)	1 (2)	2 (4)
hysterectomy +/- bilateral salpingo-oophorectomy	11 (24)	1 (2)	1 (2)
transfusions +/- vitamin K	1 (2)	3(7)	--
other surgery**	4 (9)	--	--
uterine ablation by radiologist	2 (4)	--	--
tumor embolization by radiologist	2 (4)	1(2)	--
chemotherapy	1 (2)	--	--
radiation	1(2)	1(2)	--
cannot tell/no intervention	3 (7)	--	9 (20)

* Numbers in parentheses refer to percentages and do not sum to 100% because some patients received more than one intervention.

** This category consists of 2 patients who underwent a salpingo-oophorectomy, 1 who had a laparoscopy with appendectomy, and 1 who had a myomectomy.