Spontaneous regression of angiosarcoma

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Abstract

Spontaneous regression of angiosarcoma is a rare and poorly understood phenomenon. We provide a review of seven known cases and describe an eighth case involving a 76-year-old male. This case illustrates two intriguing issues. First, the onset of this cancer occurred in the setting of tissue injury and regenerative wound healing with angiogenesis apparently gone awry. Second, the malignancy underwent a 2 year long spontaneous regression. An abscopal response was a possibility. An anti-tumor immune response was suggested by a CD8 immune infiltrate of the tumor. The results of full exome sequencing of the tumor are presented.

Background

Spontaneous regression of cancer was first noted in 1899 in melanoma and in 1901 in breast cancer by William Osler [1]. In a review of 176 well-documented cases [1,2] and another of 504 cases [3], many different tumor types were represented, but angiosarcoma was not among them. In melanoma the immune response to melanocyte antigens is thought to contribute. “Abscopal” effects are presumably due to systemic immune responses leading to regression of distant metastases that are initiated by local treatment of a primary mass, such as with irradiation or surgery.

Angiosarcomas are rare aggressive tumors of skin or deep tissues, with a 5-year survival rate of around 30% [4]. Patients are usually over 50 with male predominance [5]. A subset of angiosarcomas arises in a prior field of irradiation, such as after adjuvant radiotherapy for breast cancer. Here we present a case of a clinically aggressive angiosarcoma, with onset linked to traumatic tissue injury of 2 toes and a spontaneous remission lasting 2 years. Seven published cases of spontaneous remission in angiosarcoma are reviewed.

Materials and methods

Immunohistochemistry

Immunoperoxidase staining was performed on a Leica Bond III automated immunostainer, with CD3, CD4, CD8, PD1, PAX5 and CD138 as well as in situ hybridization for Ig-kappa and Ig-lambda light chains according to the manufacturer’s instructions (Leica Microsystems, Bannockburn, IL).

Results

Case presentation

A 76-year-old Asian man dropped a suitcase on his left foot nine months prior to diagnosis, resulting in tissue necrosis. Amputation of both toes was performed one month later. Surprisingly, pathology revealed a high-grade epithelioid angiocarcinoma positive for typical markers: CD31 (>90%), CD34 (40-100%), vimentin, factor VIII, Ki67 (72%), FLi-1, and thrombomodulin.

Margins were clear of malignant cells. Prophylactic below-the-knee amputation (BKA) was performed 3 months after the injury. Sixteen random sections from this amputation showed no evidence of malignant cells. Chemotherapy was refused. A prosthetic leg was ill tolerated, causing further injury to the stump. Recurrence of the tumor within the stump occurred nine months post injury. Five small tumors with blue skin discoloration were noted in the lower left abdominal wall, measuring 5-10 mm in diameter. A biopsy of 2 of these nodules revealed embolic angiosarcoma (Figure 1a).

MRI 12 months after the injury showed 2 masses in the stump area, the larger measuring 14 × 6 cm. Radiotherapy to the stump (57 Gy over 3 weeks) was without response. Rather, the stump ulcerated, exposing the underlying bone. At 15 months, the patient sustained an acute pathological fracture of the femur above the knee. X-rays, MRI and angiogram revealed extensive soft tissue and bone involvement. Above-the-knee amputation (AKA) was performed. Residual tumor was present, as assessed by MRI, in a) a bone, b) 2 large soft tissue masses in the thigh (Figure 2A), c) 5 small 1 cm nodules of the abdominal wall skin (biopsy proven embolic angiosarcoma). The patient requested comfort care. He took only NSAIDs for pain and Ganoderma lucidum spores once daily, which were started about 9 months after the injury.

Over the next 6 months there was gradual disappearance of the abdominal skin nodules and the 2 large palpable thigh masses, along with radiographic improvement of metastases in the femur and...
deep thigh tissues. On physical exam there were no palpable thigh masses and no abdominal wall tumors. A follow-up MRI 41 months post injury showed a) complete resolution of a large soft tissue thigh mass and fusion of 2 smaller prior masses (Figure 2). The latter mass corresponded in location to a newly palpable tender mass in the lower thigh, suspicious for recurrence. By 45 months post injury there was rapidly progressing lymphedema of all 4 limbs along with severe anemia unresponsive to steroids and the patient expired 49 months post injury.

**Radiology**

The initial MRI obtained 15 months post injury, at the time of pathological fracture of the femur, showed several large masses in the left thigh (Figure 2A and 2B). One of these masses underwent complete spontaneous resolution (Figure 2C). The two smaller masses were replaced by a new mass at follow-up imaging obtained 41 months post injury (Figure 2D), suspicious for possible recurrence.

**Pathology**

The original biopsy showed epithelioid angiosarcoma with focally prominent vascular differentiation, including focal, freely anastomosing vascular channels but also including solid areas. There were focal accumulations of hemosiderin-laden macrophages. The tumor cells showed the typical expression of CD31 and CD34 and were negative for cytokeratin and S-100. The tumor contained a focally dense infiltrate composed mainly of CD8+ T cells. These CD8 cells lacked expression of PD-1 (Figure 1b) and the tumor itself was negative for the ligand PD-L1 (data not shown). The tumor infiltrate also contained rare B cells and plasma cells, but plasma cells were focally numerous in the superficial perivascular areas remote from the tumor. Infiltrates of CD8 T cells in angiosarcoma have been previously described and are considered a favorable prognostic factor [6]. A subsequent biopsy of the 2 subcutaneous abdominal wall nodules showed focal intravascular accumulations of angiosarcoma cells (Figure 1a), while tissue from the distal aspect of the amputated leg showed diffusely infiltrative angiosarcoma cells. The cytologic features of the angiosarcoma were similar in both the original tumor and later metastases.

**Exome sequencing**

Pathology blocks, representing the initial toe amputation and 2 separate samples from the AKA amputation, had small regions of tumor rich areas, which were micro-dissected and genomic DNA was extracted. These 3 tumor samples were submitted along with the matched normal saliva sample for high depth whole exome sequencing. This analysis revealed few non-synonymous mutations with an overall mutation frequency in the tumor samples of 3.6 mutations/sequenced Mb (pre-therapy toe amputation sample; 28.4 Mb sequenced), 2.3 mutations/sequenced Mb (sample from AKA amputation; 14 months post injury; 32.7 Mb sequenced); 2.4 mutations/sequenced Mb (separate sample from AKA amputation at 14 months post injury; 32.2 Mb sequenced). There were 5 mutations that were present in each of the 3 analyzed tumor samples: KANSL1 Q941fs, RANBP2 K708R, ZNF208 S1153P, PRAMEF11 R135K and OGDHL D810G (Table 1). It is unclear whether these somatic variants contributed to the pathogenesis of angiosarcoma in this patient. We did not detect the mutations in the angiogenesis signaling pathway molecules PTPRB or PLCG1, which were reported in angiosarcomas at a frequency of 26% and 9%, respectively [7]. Analysis of rearrangements and copy number changes did not reveal tumor specific changes. Finally, the overall mutation frequency was low compared with other studies [8,9].
Table 1. Epidemiology

| Case | Year | Age/Sex | Duration of remission | Location of Angiosarcoma | Type of angiosarcoma | Reference |
|------|------|---------|-----------------------|-------------------------|----------------------|-----------|
| 1    | 1976 | 79M     | 2.5 years             | Left cheek between lower eyelid and nose | Epithelioid angiosarcoma | Jones [28] |
| 2    | 1991 | 75F     | 3 years               | Face and scalp          | Epithelioid angiosarcoma | Cerroni [29] |
| 3    | 1995 | 63F     | 6 weeks               | Forehead                | Epithelioid angiosarcoma | Brandes [30] |
| 4    | 2007 | 92M     | 3 years               | Central facial cutaneous angiosarcoma | Epithelioid angiosarcoma | Sluzevich [31] |
| 5    | 2008 | 72F     | 7 months              | Breast angiosarcoma with metastases to lung and scalp | Epithelioid angiosarcoma | Kim [23] |
| 6    | 2007 | 64M     | 6 months              | Head and neck           | Epithelioid angiosarcoma | Thong [32] |
| 7    | 2013 | 73F     | 7 months              | Subcutaneous nodule on chest | Epithelioid angiosarcoma | Tanaka [4] |
| 8    | 2015 | 76M     | 3.4 years             | Toes                    | Epithelioid angiosarcoma | Current Paper |

Table 2. Mutated genes in angiosarcoma, Case 8

| Gene | Gene name | Chrom. Freq. | Protein Change | Role | References |
|------|-----------|--------------|----------------|------|------------|
| PRAMEF1 | PRAME family member 11 | 1 3 | R135K | Retinoic acid receptor binding | NCBI |
| RANBP2 | RAN binding protein 2 | 2 3 | K708R | GTP-binding protein of RAS superfamily | NCBI |
| OGDHL | oxoglutarate dehydrogenase-like | 10 3 | D810G | Growth Modulation, activation of AKT signaling pathway | [33] |
| KANSL1 | KAT8 regulatory NSL complex subunit 1 | 17 3 | Q941fs (frameshift) | Prominent epigenetic regulator; stabilizes microtubule minus ends in a RanGTP-dependent manner. Essential for spindle assembly and chromosome segregation. | [34] |
| ZNF208 | zinc finger protein 208 | 19 3 | S1153P | Zinc finger protein, regulates gene transcription | NCBI |
| P2RX1 | purinergic receptor P2X, ligand gated ion channel, 1 | 17 2 | N204K | Function as ATP-gated ion channels | NCBI |
| GPS1 | G protein pathway suppressor 1 | 17 2 | H253R | Suppress G-protein and mitogen-activated signal transduction | NCBI |
| GAGE2A | G antigen 2A | X 2 | Q59E | Unknown | NCBI |
| TCHH | trichohyaline | 1 1 | 326_327EA>ERA (insertion) | Involved in skin morphogenesis | [35] |
| POTEE | POTE ankyrin domain family, member E | 2 1 | R910C | Unknown | NCBI |
| SLC4A3 | solute carrier family 4 (anion exchanger), member 3 | 2 1 | R1104Q | Inorganic anion exchange | NCBI |
| DCLK2 | doublecortin-like kinase 2 | 4 1 | E594_splice (splice site mutation) | Regulates microtubule polymerization and protein interaction | NCBI |
| LHFPL3 | lipoma HMGIC fusion partner-like 3 | 7 1 | N226Y | Transmembrane protein | NCBI |
| FBXW5 | F-box and WD repeat domain containing 5 | 9 1 | S558del (deletion) | Regulates DLC1, a Rho-GTPase tumor suppressor | [36] |
| PRB2 | proline-rich protein subfamily 2 | 12 1 | S52del (deletion) | Abundant protein family in saliva | [37] |
| ZFHX3 | Zinc Finger Homeobox 3 | 16 1 | R3526del (deletion) | TF regulating myogenic and neuronal differentiation | NCBI |
| KRTAP1-5 | keratin associated protein 1-5 | 17 1 | I88T | Keratin-associated protein family, forms matrix of keratin intermediate filaments | NCBI |
| POTEC | POTE ankyrin domain family, member C | 18 1 | R477Q | Possible involvement in reproductive processes | [38] |
| ZNF563 | zinc finger protein 563 | 19 1 | W298fs (frameshift) | Possible involvement in transcriptional regulation | NCBI |
| FRG1B | FSHD region gene 1 family member B, pseudogene | 20 1 | A41T | Unknown | NCBI |

Discussion

This case of angiosarcoma is unique for two reasons: a) onset of angiosarcoma in the setting of traumatic tissue injury and repair; b) dramatic spontaneous regression of angiosarcoma.

Trauma as a cause of cancer

Physiological wound healing can be followed by benign or malignant local tumors [10-14]. Angiosarcomas have been reported to arise in sites of “trauma,” including natural and surgically constructed arteriovenous fistulae, and sites of foreign bodies [15-18]. Angiogenesis regulation may be disturbed in such cases. Regulation of angiogenesis and neo-angiogenesis in tumor tissues involves many molecular mechanisms [19].

The malignant angiosarcoma cells were confined to the same 2 toes that were injured and not present anywhere else. Also, the timing of malignant transformation just 1 month after injury suggests a causal relationship.

Abscopal effect

The term “abscopal effect” refers to systemic anti-tumor effects after local radiation therapy [20,21]. The updated definition includes any type of local therapy leading to systemic effects on metastatic lesions. Abscopal effects can occur following cytoreductive surgery such as orchidectomy for prostate cancer, mastectomy for breast cancer, or nephrectomy for renal cell carcinoma [20,21]. Both abscopal effects post irradiation and post-surgical cytoreduction are likely due to immunological effects [21,22]. In the present case, systemic regression
of massive residual tumors was observed only months after AKA. Prior radiotherapy to the BKA stump was probably non- contributory as there was tumor progression.

**Spontaneous regression**

Spontaneous regression is defined as complete or partial reduction of a malignant neoplasm without treatment or with treatment deemed insufficient. Spontaneous regressions have been described in many tumor types, but angiosarcoma is conspicuously absent in several reviews [3]. The proposed mechanisms include immune responses, elimination of carcinogens, increased level of cancer cell apoptosis, hormonal influences, and epigenetics [23].

We summarize seven additional cases of spontaneous regression of angiosarcoma from the literature (Table 1). The 8 cases are all epithelioid angiosarcomas, include 4 males and 4 females, spanning ages 63-92, consistent with known epidemiology. The organ distribution is also consistent with disease characteristics [5]. Spontaneous regression lasted between 7-41 months.

**Ganoderma lucidum**

The Chinese herbal medicine, Ganoderma lucidum, also known as Lingzhi or Reishi has been reported to have anti-metastatic, anti-inflammatory, cytotoxic, cytoplastic, and immunomodulatory properties [24-26]. However, there have been few randomized controlled trials studying the fungus [26]. A meta-analysis of 5 randomized controlled trials comparing G. lucidum against placebo for various cancers showed a statistically significant increase in percentages of peripheral blood CD3, CD4, and CD8 cells without reaching statistical significance. However, G. lucidum led to spontaneous regression. Indeed, combinations of radiotherapy and immunotherapy have been of special interest recently [27,28].

The CD8 cells that infiltrated the initial tumor tissue were PD-1 negative (Figure 1b) and the tumor itself was PD-L1 negative (Figure 1b). G. lucidum can boost immune responses, its use may have enhanced the abscopal effect seen in this case leading to spontaneous regression. Indeed, combinations of radiotherapy and immunotherapy have been of special interest recently [27,28].

Angiosarcoma should be added to the list of cancers that can undergo spontaneous regression. An immunologic mechanism seems likely, implying that immune therapies might be effective in some patients with angiosarcoma.

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