

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 absopal 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. "Absopal" 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 sustaining a hairline fracture and hematomas of his 4th and 5th toes 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) 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

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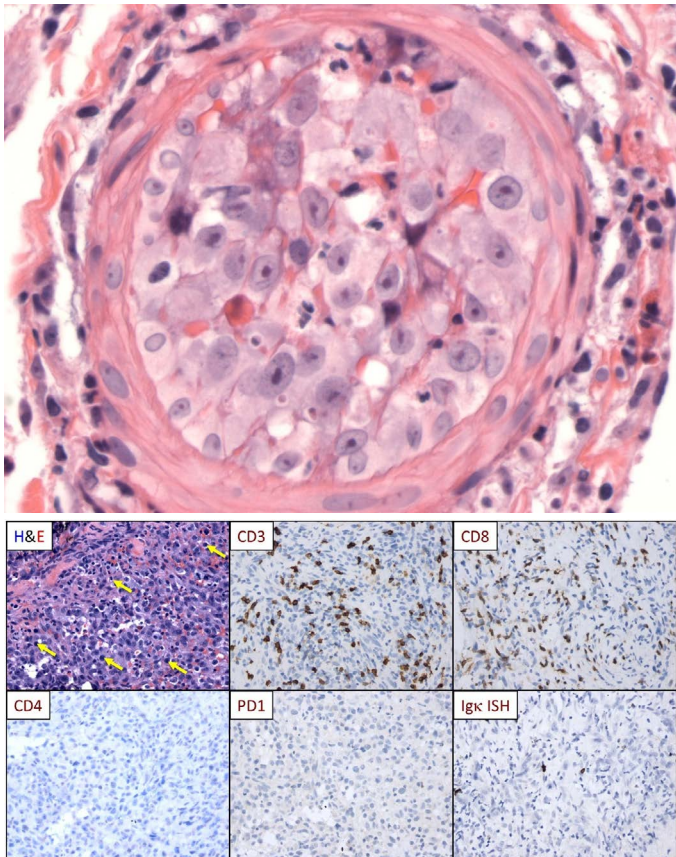


Figure 1. Immunopathology. a) H & E stain of an abdominal wall nodule showing embolic angiosarcoma completely obstructing a small arteriole. b) Immunohistochemistry (IHC), all images 200 \times . The angiosarcoma (H&E, upper left) was infiltrated by lymphoid cells (yellow arrows). IHC showed that the infiltrate was composed almost exclusively of CD3+/CD8+ T cells (negative for CD4 [lower left]). The T cells did not express PD-1 (lower middle) and the tumor cells did not express PD-L1 (not shown). The infiltrate contained only rare B cells (PAX5+, not shown) and rare plasma cells (Ig κ ISH, lower right; Ig λ ISH was similar [not shown]). Images are from the toe amputations, obtained one-month post injury (the earliest tissue samples).

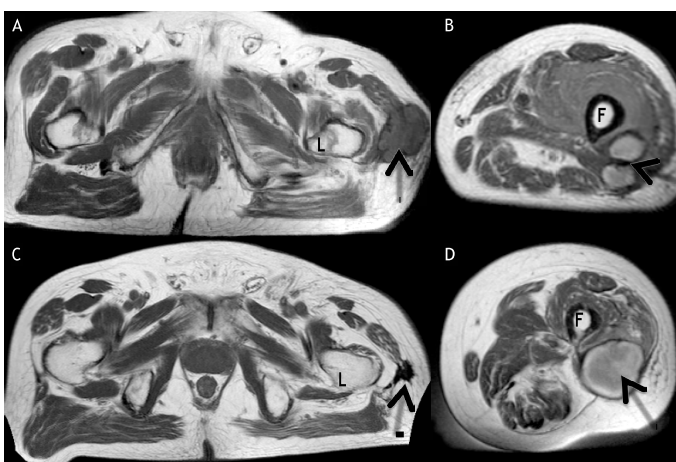


Figure 2. MRI evidence of tumor regression. 2A and 2B, Axial T1-weighted images from initial MRI reveal subcutaneous hypointense mass (arrow, 2A) posterolateral to the left femoral lesser trochanter (L), and two adjacent hyperintense masses (arrow, 2B) posterolateral to the left femoral diaphysis (F). 2C and 2D, Axial T1-weighted images from follow-up MRI demonstrate marked size/signal decrease of the mass (arrow, 2C) posterolateral to the left femoral lesser trochanter (L) as well as coalescence of the masses (arrow, 2D) posterolateral to the left femoral diaphysis (F).

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]
ZFXH3	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	W208fs (frameshift)	Possible involvement in transcriptional regulation	NCBI
FRG1B	FSDH region gene 1 family member B, pseudogene	20	1	A41T	Unknown	NCBI

Note: Freq. represents whether the mutation was found in 1/3, 2/3 or 3/3 samples submitted for exome sequencing.

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 orchiectomy 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, cytostatic, 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 greater responsiveness to chemo/radiotherapy in the *G. lucidum* group without reaching statistical significance. However, *G. lucidum* led to a statistically significant increase in percentages of peripheral blood CD3, CD4, and CD8 cells *in vivo* [26]. If *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].

The CD8 cells that infiltrated the initial tumor tissue were PD-1 negative (Figure 1b) and the tumor itself was PD-L1 negative. Thus, this immune checkpoint would have been non-functional, possibly leading to unfettered CD8 T cell expansion, similar to what occurs when checkpoint inhibitors are used.

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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