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Case Report

Metastatic Colonic Glomus Tumor, Insights in to its Pathogenetic Mechanisms. A Case Report with Comprehensive Molecular Profiling

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Abstract

We report the case of a 58-year-old male found to have hepatic metastatic disease from a primary colonic malignant glomus tumor (GT) diagnosed 4 years earlier. To the best of our knowledge, this is the first report of metastatic colonic GT in the medical English literature. GTs represent a poorly understood, rare mesenchymal neoplasm arising from a neuro-myo-arterial structure.

Interrogation of 324 genes on paraffin-embedded tissue revealed a microsatellite stable tumor with a low mutation burden (5 Mutations/Megabase), NOTCH2 rearrangement and ATRX exon duplication. NOTCH2 rearrangements have been previously described in the literature in malignant GTs. This is the first reported case of a ATRX gene mutation in a GT. ATRX gene has been previously reported in angiosarcomas and other tumor pathways as it is implicated in the alternative lengthening of telomeres. NOTCH2 and ATRX represent potential targets for therapy and decreased roles for radiation therapy and immune checkpoint inhibitors. We are intrigued by the growing evidence demonstrating benefits of combination PARP inhibitors and VEGF blockade.

The underlying pathogenesis of GT is broad and complex. After review of literature, we propose a pathway where alternative telomeric lengthening and NOTCH signaling play a central role in malignant GT transformation. This is a single case that requires further investigation into this molecular progression. As our knowledge of this tumor class advances, a more complete picture can be elucidated as well as additional lines of precision therapy.

Keywords: Glomus Tumor; Malignant Glomus Tumor; Glomangiosarcoma; ATRX; NOTCH2

Abbreviations

ATRX: A-Thalassemia/Mental Retardation Syndrome X-Linked Gene; CT: Computerized Tomography; ESI: Epidural Steroid Injection; GIST: Gastrointestinal Stromal Tumor; GT(S): Glomus Tumor(S); HPF: High Power Field; MRI: Magnetic Resonance Imaging; RFA: Radio Frequency Ablation

Introduction

Glomus tumors are a rare mesenchymal neoplasm arising from a neuro-myo-arterial structure resembling the normal glomus body. Glomus bodies are arteriovenous anastomoses found throughout the body involved in skin thermoregulation [1]. They have been classified by the World Health Organization among tumors of perivascular smooth muscle differentiation [2].

The first report of a GT dates back to 1812, when Wood described it as a painful subcutaneous tubercle [3]. It wasn't until 1988 when the first report of colonic GT was made by Barua [4]. To the best of our knowledge, this is the first report of a metastatic colonic GT in the English medical literature.

Case Report

A 54-year-old male with past medical history of bipolar disorder, presented at our institution with complains of abdominal discomfort of 6-month duration, bright red blood per rectum with pencil-like thin stools and a non-intentional 13 kilo weight loss. Laboratory testing was only remarkable for hemoglobin of 10.2 mg/dl (adult male reference range: 13.5 to 17.5 mg/dl). Colonoscopy and CT scans were performed showing a 4 cm mass, involving the distal transverse and proximal descending colon. The patient underwent surgical resection of the mass with no complication.

Pathological exam of the colonic resection specimen showed a polypoid mass, measuring up to 3.8 cm (Figure 1). Microscopic evaluation revealed sheets and nests of pleomorphic tumor cells involving the colonic submucosa and muscularis propria. The tumor cells exhibited round to ovoid nuclei with irregular nuclear borders, and prominent nucleoli with coarse chromatin. The cell borders were well defined, with a slightly eosinophilic cytoplasm (Figure 2). The mitotic count was high, reaching up to 20 mitotic figures per 50 HPF. No lymph vascular invasion or perineural invasion was present. Immunohistochemical studies showed that the tumor cells were positive for smooth muscle actin and h-salesman, both markers of smooth muscle differentiation; and negative for CD34, CD117, DOG-1, S-100, cytokeratin's, desmin, HMB-45, synaptophysin and chromogranin. The cytologic atypia, large tumor size (3.8 cm), visceral location and high mitotic rate warranted the diagnosis of malignant colonic GT.

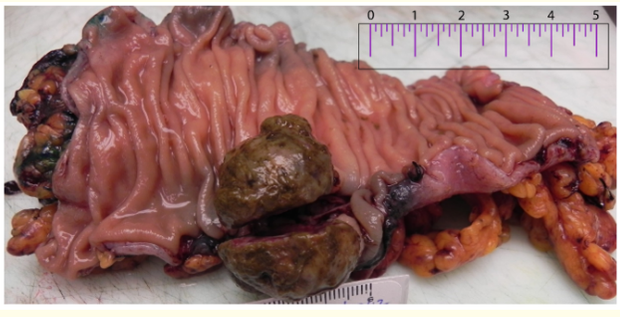

Figure 1: Photography of colonic resection specimen. Gross photography of colon resection specimen showing a tan, polypoid mass, that measured up to 3.8 cm.

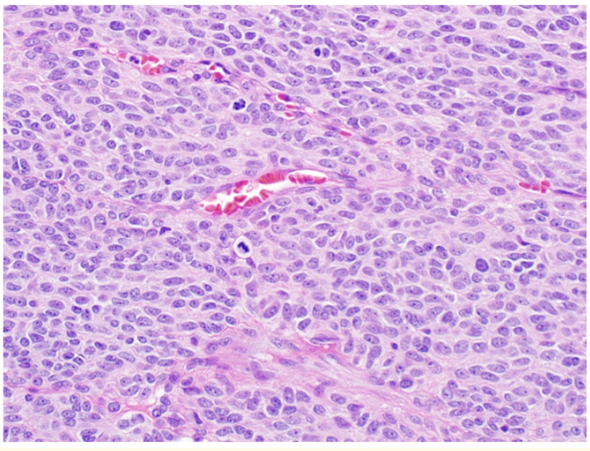

Figure 2: Microphotography of colonic glomus tumor. H&E stained tissue showing sheets ofpleomorphic tumor cells with irregular, round to ovoid nuclei with prominent nucleoli, and well defined cell borders, with slightly eosinophilic cytoplasm, in a vascular background. There is a mitotic figure on the center of the image. (400x).

Unfortunately, after the surgical resection, the patient was lost to follow-up, returning 4 years after the initial diagnosis. This time with metastatic tumor to the liver. MRI showed three liver masses, measuring up to 8 cm. All the lesions were localized on the right hepatic lobe, amenable for surgical resection which was performed after two cycles of chemotherapy with Adriamycin and Isofosfamide. Repeat imaging after chemotherapy showed no change on tumor size. Microscopic exam of the hepatic lobectomy specimen showed increased tumor atypia and mitotic activity, with up to 50 mitotic figures per 50 HPF, (Figure 3 and 4). The same immunohistochemical panel performed of the colonic tumor was repeated on the liver metastases rendering the same results. At this time a diagnosis of metastatic malignant GT was confirmed.

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on the liver metastases rendering the same results. At this time a diagnosis of metastatic malignant GT was confirmed.

In hopes of finding treatment/palliative options interrogation of 324 genes on paraffin-embedded tissue was performed, revealing a microsatellite stable tumor with MLL2 R2635Q mutation, a low mutation burden (5 Mutations/Megabase), NOTCH2 rearrangement intron 26 and ATRX exon 9-15 duplication. Regrettably, our patient did not qualify for any of our clinical trials for targeted therapy and went on into hospice care.

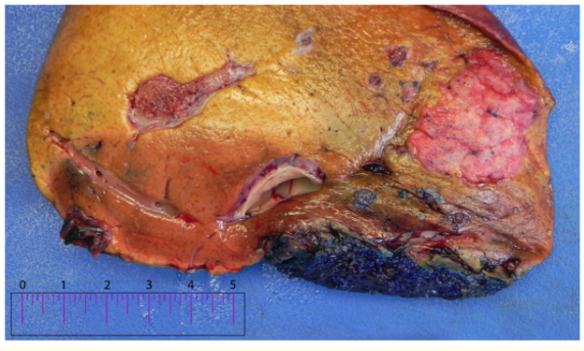

Figure 3: Photography of liver resection specimen. Gross photography of the right hepatic lobe resection specimen showing an intraparenchymal well defined, pink-tan tumor nodule that measured up to 2.8 cm. No necrosis or hemorrage was present on the specimen.

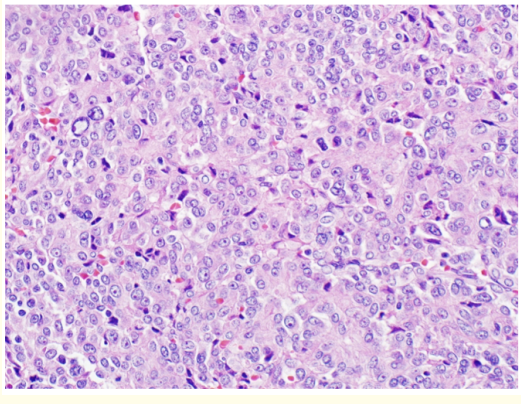

Figure 4: Microphotography of metastatic colonic glomus tumor to the liver. H&E stained tissue showing sheets of tumor cells with strikingly atypia and numerous mitotic figures. Note the large nuclear pleomorfism of the cells on the left uppen corner. (400x).

Discussion

GTs account for < 2% of soft tissue tumors [5]. Primary colonic GTs are exceedingly rare and little is known about their natural history. Most glomus tumors are benign, and cured by simple excision but reports of atypical, infiltrative, malignant-appearing, and metastatic glomus tumors have led to efforts of trying to elucidate a classification of GTs showing aggressive behavior or unusual morphology in an attempt to better risk stratify patients in order to provide the best therapeutic approach.

In 1990, Gould., *et al*. [6] first proposed criteria for the classification of malignant GTs. This was later further expanded and refined by Folpe., *et al*. in 2001 [7], with a case series review of 52 atypical or malignant GTs. These findings lead to the current 2013 World Health Organization (WHO) classification, where GTs are classified as (a) typical GT, (b) simplistic (c) glom angiomatosis (d) GT of uncertain malignant potential and (e) malignant GT or glom angiosarcoma [8].

According to this last classification, the diagnosis of malignant GT is reserved for those tumors with marked nuclear atypia and any level of mitotic activity, or tumors with atypical mitotic figures, or tumors larger than 2 cm at deep locations. These are highly aggressive tumors with metastases found in approximately 40% of cases. Since the publication of this classification, there is at least one case report on a metastasizing GT of low malignant potential [9], suggesting that further study into this neoplasm is needed, and perhaps looking into its molecular pathways might be of aid.

The underlying pathogenesis of GTs is largely unknown, with the familial forms having a better understood genetic pathway. In 2002 Brouillard., *et al*. [10] described the glomalin gene located in 1p22.1, They postulated that inactivating mutations, in a two-hit sequence, at this location is behind familial glomangiomas. In 2009 Brems., *et al*. [11] proposed the biallelic inactivation of NF1 gene as a possible mechanism for the development of GT in the context of neurofibromatosis.

Sporadic cases have a less well understood pathophysiology with several genes reported to be altered. A series of 102 GTs [12] detected BRAF V600E mutation in 6% of GTs, all of which were malignant GT or GT of low malignant potential, suggesting that this mutation could be associated with a malignant phenotype and offering a possible target of therapy. Other oncogenic mutations have been reported as well, like KRAS G12A, detected on a case of GT involving the finger [13].

NOTCH gene family rearrangements and fusion genes have also been described in GTs [14]. NOTCH3 rearrangements were identified in 9% of benign GTs in a series of 33 GTs [14]. In this same case series, NOTCH2 gene rearrangements were identified in 52% GTs, including all malignant GTs [14].

NOTCH2 has also been described as an important oncogene in other tumor types such as bladder [15], and hepatocellular carcinoma [16]. It is postulated that downregulation of NOTCH2 will inhibit tumor cell proliferation and increase their sensitivity to 5-Fluorouracil [16], making it a potential target for therapy. In this regard the NOTCH2 inactivating antibody NRR2Mab [16] and NOTCH pathway inhibitors, like LY900009 [17] are potential therapeutic agents.

Our case presented an ATRX exon 9 - 15 duplication, to the best of our knowledge, this is the first report of an ATRX gene mutated GT. ATRX is a chromatin remodeling protein belonging to the SWI/SNF family, implicated in alternative lengthening of telomeres, especially in tumors of mesenchymal origin [18-19]. This could potentially lessen the role of radiation therapy [20-21] in these tumors, emphasizing the need of finding targets for therapy. In this regard, an ongoing phase 1 clinical trial (Clinicaltrials.gov NCT03842228) with PARP inhibitors and VEGF blocking agents seems promising.

Discussion

The pathological differential diagnosis of GTs includes GIST, melanoma, neuroendocrine tumors, paraganglioma, low grade lymphoma and hemangiopericytoma. Morphology and immunohistochemical characteristics might aid us in making this diagnosis. Glomus cells are uniform, small, round cells with a central, round nucleus and amphophilic or lightly eosinophilic cytoplasm. Each cell is surrounded by basal lamina, best highlight by PAS or toluidine blue histochemical stains. Glomus cells classically express smooth muscle actin and have abundant pericellular type IV collagen production. H-caldesmon is also positive, whilst desman, CD117, cytokeratin's, CD31, HMB-45, Melan-A, CD56, chromogranin and S100 protein are usually negative [6,22]. CD34 and synaptophysin have been reported to be focally, weakly positive in a few gastric GT cases [22].

The underlying pathogenesis of GTs is extensive and complex. After review of literature, we believe the pathogenesis of this neoplasm, specially its malignant transformation might be closely related to hyperactivation of the MAP-Kinase pathway. Genetic interrogation of KRAS, BRAF,NOTCH and SWI/SNF family genes could perhaps be of aid in selected cases when assessing the patient's risk of malignancy. As our knowledge of this tumor class advances, a more complete picture can be elucidated as well as additional lines of precision therapy.

Conflict of Interest

The authors have no financial interest or any conflict of interest.

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