Case Report:
Plasma Cell Neoplasm in Conjunction with Glioblastoma of the Conus Medullaris

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Abstract. We report a plasma cell neoplasm in conjunction with a glioblastoma multiforme (GBM) of the conus medullaris in a 42-year-old man. Glioblastoma is a World Health Organization (WHO) grade IV neoplasm that requires surgical intervention, radiation, and possibly chemotherapy. Astrocytomas of the spinal cord are rare neoplasms, with intramedullary glioblastomas comprising only 1% to 3%. Plasma cell neoplasms result from monoclonal proliferation of mature B cells; they have been reported as a primary malignancy with gliomas arising after treatment. Secondary plasma cell neoplasms arising within glioblastomas have not previously been described. However, there have been reports of glioblastomas related to other plasma cell and hematopoietic diseases such as Waldenstrom's macroglobulinemia and myeloid sarcomas.

Introduction
Glioblastoma is a high grade (WHO IV) glial neoplasm of the central nervous system. It is characterized by an abundance of highly pleomorphic astrocytes that possess marked nuclear atypia and mitotic activity with microvascular and endothelial cell proliferation and/or necrosis [1]. Glioblastomas occur at any age but are most common between 45 to 75 years, with the majority located in the cerebral hemispheres [1]. Plasma cell neoplasms include a group of diseases that result from the monoclonal expansion of immunoglobulin-producing B cells. These neoplasms include monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's macroglobulinemia, plasma cell myeloma and its variants, solitary plasmacytoma of bone, extramedullary plasmacytoma, immunoglobulin deposition diseases, and osteosclerotic myeloma [2]. These disorders involve various sites of the body and have been associated with connective tissue diseases, peripheral neuropathies, and other skin, endocrine, or liver diseases, as well as following solid organ or bone marrow transplantation [2]. We report the unique presentation of a plasma cell neoplasm in the spinal cord after two resections and therapy for a glioblastoma of the conus medullaris.

Case Report
A 34-yr-old man initially presented to his physician with complaints of radiating pain in the right buttock and leg. His medical history included arthroscopic knee surgery; he had no other pertinent medical or family history. He received a series of epidural blocks that provided temporary relief of his pain, and during the following six months he developed a right foot drop. Magnetic resonance imaging (MRI) in October 2000 revealed a 3.8 x 1.9 cm intradural, intramedullary lesion with limited enhancement that nearly filled the spinal canal. There was no disc protrusion or nerve root compression. Partial resection of this mass revealed hypercellular glial tissue with mild degeneration in the conus medullaris.
nuclear pleomorphism consistent with a well differentiated astrocytoma (WHO grade II). After surgery, he received external beam radiation, but he continued to have worsening pain that was unresponsive to analgesic therapy.

In April 2007, the patient developed incontinence and persistent low back pain radiating to his groin. A hydromorphone hydrochloride pain pump was inserted for management, but his symptoms continued. In September 2007, an MRI study showed an increase in the mass from 2.0 x 1.2 x 1.2 cm to 2.0 x 2.0 x 3.7 cm with significant filling of the spinal canal (Fig. 1). Debulking of the tumor in September 2007 confirmed recurrence of the glial neoplasm, which possessed scattered spindled tumor cells associated with malignant gemistocytes and uninucleated and focal multinucleated tumor cells. There was cellular pleomorphism and endothelial cell proliferation. Isolated hemorrhage and necrosis were present. In addition, hyalinizing fibrosis was associated with focally prominent vasculature and chronic inflammation including lymphoid cells, plasma cells, and scattered macrophages. The glial fibrillary acidic protein (GFAP) immunostain was strongly positive. The Ki-67 immunostain varied from <2% to focal 20% positivity (Fig. 2). These findings were consistent with a glioblastoma of the conus medullaris. Temozolomide therapy was initiated at a dose of 200 mg/m². The patient experienced bruising, with his platelet count dropping to 9,000/dl in February 2008. At that time temozolomide therapy was stopped, but a second cycle at 150 mg/m² was begun when the thrombocytopenia resolved.

Progressive paraplegia occurred over the following months. In November 2008, MRI studies revealed that the tumor diameter had increased to 3 cm. Surgical removal

Fig. 2. Ki-67 (200x) positive staining of glia in the 2007 GBM, compared to 2-3% staining of the 2000 astrocytoma (inset).
Fig. 3. H&E stain (600x) demonstrating cellular pleomorphism and mitoses (arrows) in the 2008 GBM.
Fig. 4. H&E stain (200x) demonstrating necrosis in the 2008 GBM.
Fig. 5. H&E stain (400x) demonstrating sheets of plasma cells within the 2008 GBM with CD 138 positive staining (inset).
of the tumor to preserve the patient's life included a T8-S1 laminectomy in November 2008, with removal of the T8 spinal cord down to the cauda equina. Initial H&E-stained sections showed recurrent glioblastoma (Figs. 3, 4) with sheets of plasma cells (Fig. 5). The tumor specimen was stained for GFAP and CD 138 antibodies using an automated immunohistochemical technique with epitope enhancement, and it was stained for kappa and lambda messenger RNA via non-isotopic in situ hybridization (ISH). These stains demonstrated GFAP positivity of the pleomorphic glial cells in the glioblastoma multiforme (Fig. 6), with sheets of plasma cells decorated with CD 138 antibody (Fig. 5 inset). These plasma cells had monoclonal expression of kappa messenger RNA (Fig. 7), with very few plasma cells that stained for lambda messenger RNA.

To define this clonal plasma cell neoplasm, additional antibody stains were done including MUM-1, cyclin D1, CD 20, PAX-5, IgG, IgM, IgA, and CD 19, using appropriate epitope enhancement. The plasma cells stained positively with MUM-1 and CD 19 (Fig. 8), and monoclonal IgD (Fig. 9); there were scattered CD 20 positive cells. The CD 20 positivity raised the possibility of a marginal zone lymphoma with plasmacytic differentiation. Examinations failed to reveal an M protein in the patient's urine or blood, and his blood counts remained in the appropriate range. Bone marrow aspiration failed to reveal any features of multiple myeloma or lymphoma. These immunohistochemical and laboratory findings favored a diagnosis of a plasma cell neoplasm in conjunction with a glioblastoma of the conus medullaris. A marginal zone lymphoma with plasmacytic differentiation could not be excluded.

Immunotains for PAX-5, CD 138, CD 3, CD 20, p53, IgD, Ki-67, and ISH for kappa and lambda were performed to elucidate the progression of the astrocytoma to glioblast-
Spinal cord astrocytomas are rare neoplasms of astrocytes that are immunoreactive for GFAP. Increased proliferative activity is evident in high grade tumors with Ki-67/MIB-1 mean values of 15% to 20% [1]. Our patient’s tumor possessed prominent GFAP expression and a Ki-67 label of 2 to 3% in the initial tumor, which was consistent with a low grade astrocytoma (WHO grade II). The 2008 recurrent tumor, with Ki-67 labeling focally approaching 20%, also had necrosis and endothelial cell proliferation, warranting the diagnosis of glioblastoma. Despite multiple resections and chemoradiation, the tumor recurred on two occasions.

Spinal cord astrocytomas are rare neoplasms that require surgical treatment and may necessitate radiation and chemotherapy. Glioblastoma multiforme comprises about 1% to 3% of intramedullary spinal cord gliomas and is diagnosed based on the degree of cellular pleomorphism, mitoses, endothelial cell proliferation, and/or necrosis [9-11]. Surgery and radiation are initial treatments, however, high-grade lesions with infiltrative borders may be difficult to resect. Local or leptomeningeal dissemination will necessitate chemotherapy [3].

With an incidence of only 0.8 to 2.5/100,000, chemotherapeutic options for spinal cord astrocytomas have not been well investigated [3]. Since 1999, phase II and III trials have reported the benefits of temozolomide in patients with WHO grade III astrocytomas and in first relapse patients with a glioblastoma [4-8]. Temozolomide is an alkylating agent that is hydrolyzed to methyl-triazeno-imidazole-carboxamide (MTIC) and subsequently to the inactive 5-aminoimidazole-4-carboxamide (AIC) and the alkylating methyl diazonium cation. This cation methylates DNA and is responsible for the cytotoxicity [4]. Myelosuppression has been reported in patients including lymphopenia (55%), thrombocytopenia (4-19%), neutropenia (8-14%), and leukopenia (11%) [4]. While cytopenias are a recognized complication of this drug, there are few reports of secondary lymphoproliferative disorders. Plasmacytomas have not been described.

Plasma cell neoplasms result from the monoclonal expansion of a mature, immunoglobulin-secreting B-cell that possesses both CD 19 and CD 138 antigens. Immunoglobulins are comprised of kappa or lambda light chains and a class-identifying heavy chain (IgM, IgA, IgD, IgE, IgG). The MUM-1 and scattered CD 20 positive cells classify this lesion as a B-cell neoplasm, raising the possibility of a diffuse large B cell or marginal zone lymphoma with plasmacytic differentiation [12]. In view of the benign clinical follow-up, the unusual extranodal location, and IgD kappa expression, extramedullary plasmacytoma may be favored, but differentiation between the two is extremely difficult.

Secondary malignancies that develop after aggressive treatment for a primary malignancy have been well described. Leukemias have been reported following the use of alkylating agents and epipodophyllotoxins [13,14]. CNS gliomas have appeared after radiation therapy for a primary malignant neoplasm [15,16]. Myelodysplastic syndromes and acute myeloid leukemia have occurred following temozolomide therapy for gliomas [17]. Our patient received both treatments and developed a plasma cell proliferation with monoclonal expression of IgD.

Rare cases of Waldenstrom’s macroglobulinemia associated with a cerebral glioblastoma have been reported, with some diagnosed simultaneously [18,19]. Diffuse non-monoclonal plasmacytosis has been reported following multi-agent chemotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) [20]. Recently, a myeloid sarcoma within a glioblastoma was reported in a patient with a previous history of acute myelogenous leukemia [21]. In addition, gliomas occurring in patients with previous lymphoid malignancies include some glioblastomas complicating the course of myelomas [22-25]. Lymphoid proliferations may have some effect on vascular permeability and susceptibility of degenerated white matter to reactive gliosis [19]. While plausible, our case defies such reasoning because the astrocytoma and glioblastoma were lesions that arose years before the plasmacytic proliferation occurred. This is the first reported case of a plasma cell neoplasm arising in association with a glioblastoma in the conus medullaris.

Acknowledgements
We thank Sheron Lear and Clinical Pathology Associates in Louisville, Kentucky, for assistance with the immunohistochemical stains.

References
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