Molecular Association of Medulloblastoma and Sarcoidosis: Case Report and Review of the Literature

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Key words
- Leukotriene
- Medulloblastoma
- Sarcoidosis
- Sonic hedgehog gene

Abbreviations and Acronyms
CNS: Central nervous system
MB: Medulloblastoma
MRI: Magnetic resonance imaging
SHH: Sonic hedgehog
SNP: Single nucleotide polymorphism

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BACKGROUND: **Medulloblastoma (MB) is a malignant tumor of the central nervous system (CNS), and sarcoidosis is a chronic inflammatory disease of many organ systems, commonly affecting the lungs. No association between MB and sarcoidosis was described in the literature. MB and sarcoidosis have mutual molecular and signaling pathways that may predispose patients with sarcoidosis to develop MB. We describe a patient with sarcoidosis who developed MB.**

CASE DESCRIPTION: **The patient is a 36-year-old diagnosed with pulmonary sarcoidosis presented with ataxia, bilateral horizontal nystagmus, diplopia, and bilateral upper limb dysmetria was found to have a cerebellar mass on magnetic resonance imaging (MRI). He was initially treated with corticosteroids as a case of neurosarcoidosis. The patient's symptoms worsened, and repeat MRI showed an increase in the tumor size with hydrocephalus. External ventricular drain insertion plus midline suboccipital craniotomy and resection of the tumor was performed. Pathology revealed MB classic type, sonic hedgehog–activated. There was no cerebrospinal fluid dissemination. He received craniospinal radiation and chemotherapy. Follow-up 20 months after radiation revealed residual neurologic symptoms and no recurrence on MRI brain.**

CONCLUSIONS: **The exceedingly rare coexistence of adult MB and sarcoidosis may have a causal relationship based on specific common molecules. Leukotrienes, stimulation of astrocytes and Purkinje neurons, and the sonic hedgehog signaling pathway can be considered. Further genetic and molecular studies are merited.**

INTRODUCTION

Sarcoidosis is an idiopathic inflammatory disease characterized by the presence of noncaseating granulomas on histopathology.[1,2] Multiple organ systems are affected, such as the pulmonary, lymphatic, hepatic, skin, cardiac, and central nervous system (CNS).[1] Patients with sarcoidosis who develop CNS involvement account for 5%–15%; isolated CNS involvement is rare and accounts for 1% of cases.[1,3] Multiple case reports described the presence of cerebral intraparenchymal mass lesions composed of inflammatory cells in neurosarcoidosis, and uncommonly, intraparenchymal cerebellar lesions.[4] No description of medulloblastoma (MB) associated with sarcoidosis was published in the literature. Both diseases share specific molecular and signaling pathways that may predispose patients with sarcoidosis to develop MB.[5] We describe a case of a 36-year-old man who developed MB 5 months after he was diagnosed with sarcoidosis.

Case Description

The patient is a 36-year-old man diagnosed with pulmonary sarcoidosis in April 2017 managed with corticosteroids and Imuran presented with visual blurring associated with unsteady gait and dizziness, especially early morning that started in October 2017. Neurologic examination showed horizontal diplopia and horizontal nystagmus bilaterally. Bilateral upper limb dysmetria was noticed, in addition to left abnormal rapid alternating movements and intention tremors. Ataxia was present with broad-based gait. Magnetic resonance imaging (MRI) showed a midline cerebellar lesion with an extension to the left hemisphere (Figure 1). The patient was tentatively diagnosed with neurosarcoidosis; he was restarted on corticosteroids and immunosuppressant with close follow-up. The neurologic symptoms temporarily improved; however, in March 2018, there was a relapse of neurologic symptoms with an increase in the mass size and compression of the fourth ventricle with hydrocephalus on repeat MRI (Figures 2 and 3).

The patient then underwent midline suboccipital craniotomy and total excision of the tumor with an insertion of external ventricular drain. Surgical pathology revealed a MB, classic type histology, and sonic hedgehog (SHH) molecular subtype. Postoperative computed tomography was

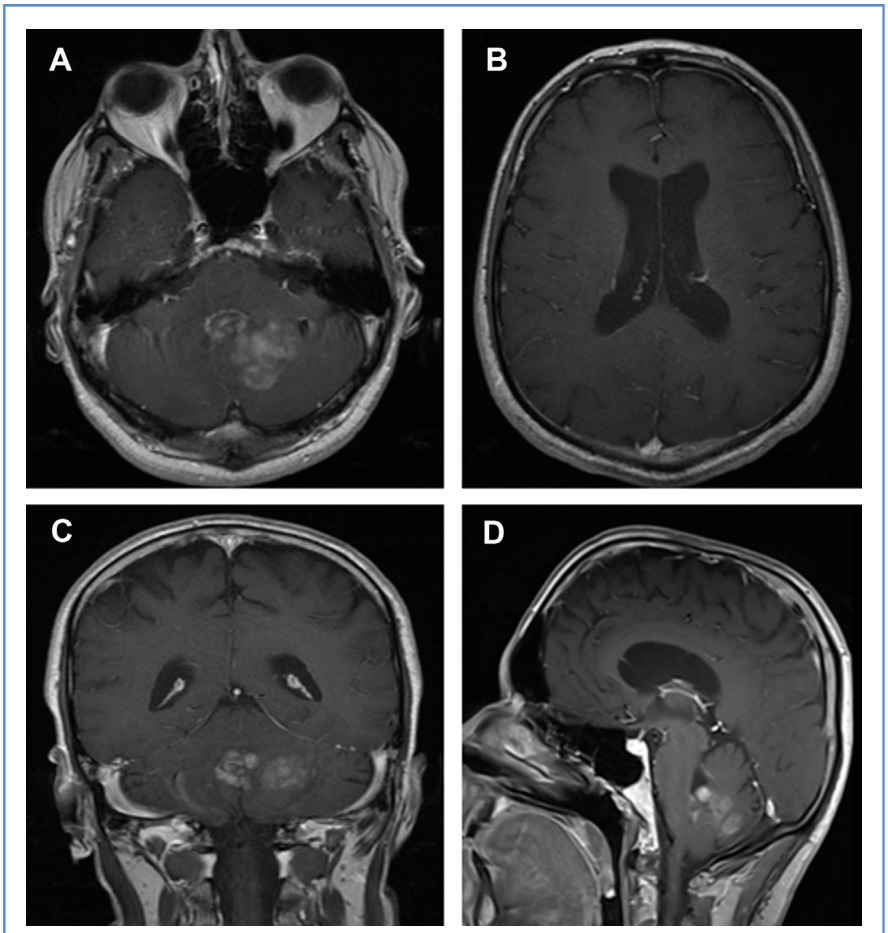

Figure 1. Axial (**A** and **B**), coronal (**C**), and sagittal (**D**) magnetic resonance imaging T1 (April 2017) with contrast showing enhancing midline and left hemispheric cerebellar mass extending to the fourth ventricle. There is mild ventricular dilation.

unremarkable, and the external ventricular drain was removed after a challenge test 3 days later. There was no tumor dissemination on spinal MRI and cerebrospinal fluid studies. The patient was discharged with residual left upper limb intention tremor, ataxia, and left eye horizontal diplopia and nystagmus. He received craniospinal radiation, and chemotherapy consisted of cisplatin, vincristine, and lomustine. Follow-up MRI brain in January 2020 showed no residual tumor (Figure 4). The patient still has persistent left upper limb intention tremor, ataxia, and left eye horizontal diplopia and nystagmus in the last follow-up.

Whole-exome sequencing was performed on this patient's tumor by amplicon-based library enrichment sequencing using Ion Torrent technology. An oncogenic somatic mutation was identified in *DDX3X* gene (NM_001356.4:exon10: c.1025+10A>T, p.Lys342_Splice, VAF 28%). No pathogenic mutations were detected in *CTNNB1*, *SMO*, *TERT*, or *TP53*.

In addition, a germline single nucleotide polymorphism (SNP) was detected in this patient's tumor in the cysteinyl leukotriene receptor 1 gene (*CYSLTR1*) (NM_001282186:exon2: c.927C>T: p.Phe309Phe, VAF 94%, rs320995).

A homozygous germline polymorphism was also identified in the nucleotide oligomerization domain (*NOD2*) (also known as *caspase recruitment domain* [*CARD15*] gene) (NM_022162:exon4: c.802C>T: p.Pro268Ser, VAF 96%, rs2066842).

DISCUSSION

Sarcoidosis is a chronic inflammatory disease with T-cell infiltration into multiple solid organs, primarily the lungs.[6] Multiple malignancies are associated with sarcoidosis, such as hematologic (leukemia and lymphoma), skin (melanoma), and solid organ tumors (lung, breast, renal, rectum, and ovarian tumors).[6] Sarcoidosis of the CNS can produce solid masses comprised of T-cells and noncaseating granulomas that mimic brain tumors. Rare cases were reported of cerebellar intraparenchymal masses that were diagnosed as neurosarcoidosis after lesion biopsy.[1,7]

MB is a malignant tumor arising from the external granular layer of the cerebellum, a highly proliferative layer that gives rise to 90% of cerebellar neurons; MB is considered the most common CNS malignancy in pediatrics.[8] MB is uncommon in adults, and approximately 80% occur in adults <40 years of age.[9,10] The current classification of MB is based on molecular types, with a more accurate age of onset and prognosis than the histopathology counterpart. Wnt, SHH, type 3, and type 4 are the current molecular types, with SHH as the most common MB occurring in adults.[11] The loss-of-function mutation in *DDX3X* found in our patient is reported in approximately 60% of *SHH* subgroup MBs in adults.[12] *DDX3X* mediates cell cycle control by regulating translational initiation of key cell cycle proteins, including cyclin E1 and hypoxia-inducible genes, and function as a tumor suppressor gene.[13]

SHH is an essential signaling pathway for the proliferation of neural progenitor cells and is formed by Purkinje cells; the absence of SHH leads to apoptosis of neural cells in the developing cerebellum.[8,14] SHH is also secreted by astrocytes and plays a vital role in sustaining MB cell proliferation through activation of SHH ligands and biosynthesis of leukotriene from MB tumor cells.[15] Leukotriene molecules then stimulate the same MB tumor cells and express nestin, an intermediate filament protein integral for MB cell proliferation and survival.[15]

In addition, SHH was found to play a role in MB proliferation through

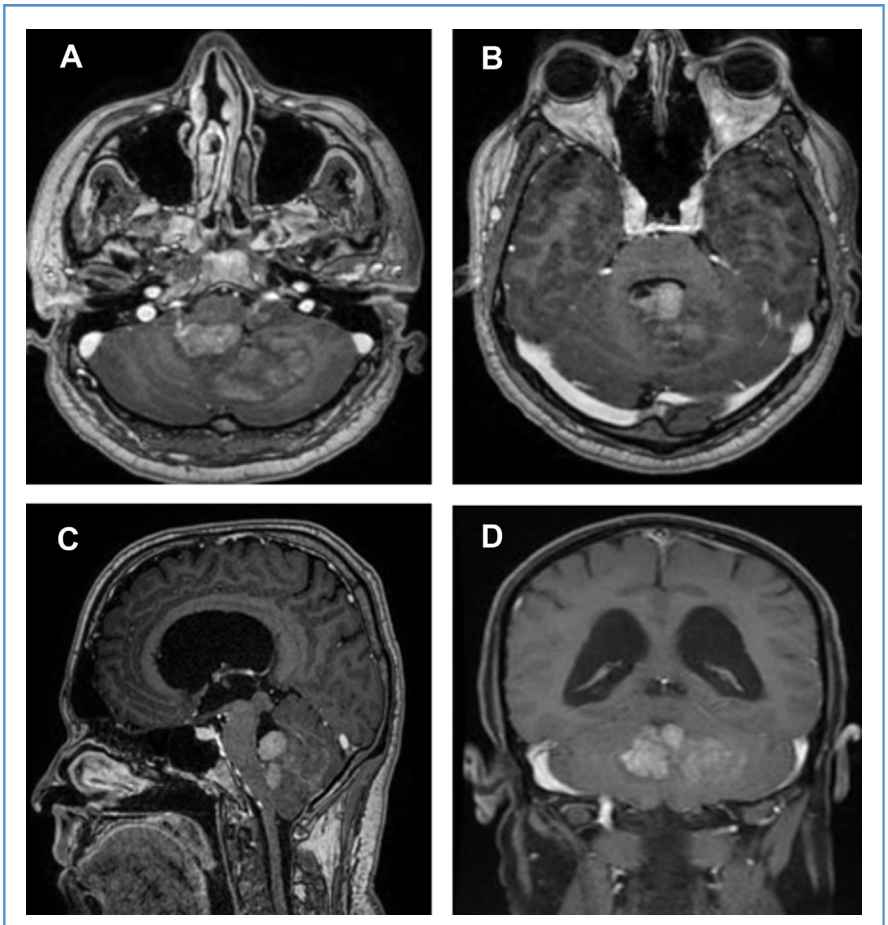

Figure 2. Axial (**A** and **B**), sagittal (**C**), and coronal (**D**) magnetic resonance imaging T1 with contrast (March 2018) showing larger lesion size with a further extension to the left cerebellar hemisphere and fourth ventricle, abutting the dorsal pons and medulla with resultant noncommunicating hydrocephalus.

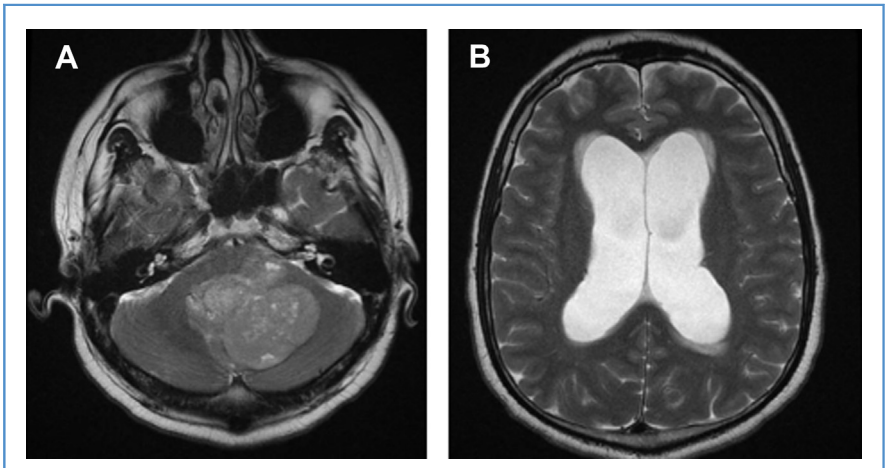

Figure 3. Axial magnetic resonance imaging T2 (March 2018) shows the midline cerebellar lesion size with no surrounding vasogenic edema (**A**). There is associated hydrocephalus (**B**).

overexpression of peroxisome proliferator-activated receptors on MB tumor cells, especially peroxisome proliferator activated receptors γ, and if bound by leukotriene, nestin synthesis increases.[15] Leukotrienes are inflammatory mediators produced by activated leukocytes and are essential for leukocyte migration, chemotaxis, and other biological functions. They are abundantly secreted in sarcoidosis. Cysteinyl leukotrienes and leukotriene B4 are exuded from the sarcoid $CD4^+$ T cells. They can be detected in the bronchoalveolar lavage of patients with pulmonary sarcoidosis.[16-18]

There are 2 types of G protein–coupled cysteinyl leukotriene receptors: CYSLTR1 and CYSLTR2, located in neurovascular endothelium, glial cells, and several types of neurons.[19,20] Leukotrienes are known to increase the blood–brain barrier permeability. They induce astrocyte proliferation and Purkinje neuron excitation.[21-23] Stimulated astrocytes, in turn, release leukotrienes.[22,24] The synonymous SNP in the CYSLTR1 detected in this patient tumor has been reported to be associated with an increased risk of asthma and plays a role in pharmacogenetics of the leukotriene pathway.[25,26] CYSLTR1 was expressed in astrocytoma, ganglioglioma, and metastatic adenocarcinoma, and in the neuron and glial-appearing cells around brain tumors.[27]

The other SNP in the NOD2 gene present in this patient tumor has shown to alter the balance between pro- and anti-inflammatory cytokines, modulating the risk of infection, chronic inflammation, and cancer.[28] This same polymorphism is reported to be associated with severe pulmonary sarcoidosis.[29] These 2 SNP alterations that are known to modulate immune responses with interleukins and other cytokine overproduction and subsequently increase the risk for infection, inflammation, granuloma formation (such as sarcoidosis), and possibly cancer. We postulate that the interactions between these SNPs, and perhaps other SNPs, have a remarkable effect on the immune dysregulation and tumor progression.

We also hypothesize that leukotriene leads to developing MB and probably other malignancies in the body in patients with sarcoidosis. The produced leukotrienes in the diseased lung make their way to the

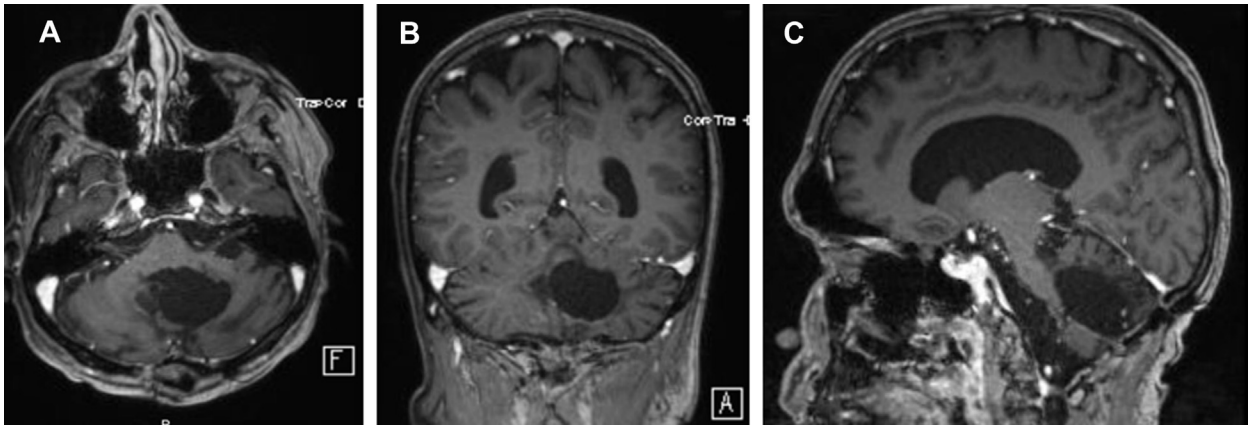

Figure 4. (**A**–**C**) Follow-up magnetic resonance imaging T1 with contrast in 2020, showing no recurrence of medulloblastoma and normal ventricular size.

blood and then stimulate the cerebellar astrocytes and Purkinje neurons with subsequent overexpression of the SHH gene and aberrant activation of the SHH signaling pathway. The resulting MB cells from the SHH pathway will start proliferating. The locally produced leukotrienes, mainly synthesized from astrocytes, will aid in the proliferation and progression of MB through nestin expression.

CONCLUSIONS

The development of MB in an adult patient with pulmonary sarcoidosis is considered extremely rare. The relationship between the 2 diseases can be explained either based on the rare mere concurrent occurrence or due to a primary disease that predisposes to another disease. Considering that leukotriene is a common factor in both diseases, it might play a role in MB tumorigenesis through the SHH pathway. The imbalanced cytokines production may promote tumor progression through immune modulation. The subject deserves further insight, genetic and molecular studies.

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