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Restricted Diffusion of Pus in the Subarachnoid Space: MRSA Meningo-Vasculitis and Progressive Brainstem Ischemic Strokes – A Case Report

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Key Words
Diffusion weighted imaging · Magnetic resonance imaging · Extra-axial · Meningitis · Vasculitis · Brainstem stroke · MRSA

Abstract
Extra-axial restriction on diffusion weighted imaging (DWI) is an unusual finding on brain magnetic resonance imaging (MRI). Intra-axial restriction on DWI, however, is common, and can represent brain parenchymal infarction, tumor, abscess, or toxic-metabolic process. The infrequency of extra-axial DWI restriction and the paucity of clinico-pathological correlation in the literature limit its differential diagnosis. Scant case reports suggest that extra-axial DWI restriction could be a lymphoma, neurenteric cyst, or, in one patient, subdural empyema [1–3]. We postulate that pus formation must be excluded first, because it can provoke an aggressive meningo-vasculitis with rapidly fatal, intra-axial infarctions. Our patient was a 45-year-old man, presenting to our hospital with left facial droop and right (contralateral) arm and leg weakness. Initial MRI revealed DWI restriction in the left lateral pons, consistent with a classic Millard-Gubler stroke. Also noted was a subtle, extra-axial area of curvilinear diffusion restriction in the left cerebellar-pontine angle's subarachnoid space. Days later, the patient had a headache, and repeat MRI revealed extension of the two DWI lesions – both the intra-axial pontine infarction and the extra-axial area of restricted diffusion in the subarachnoid space. The patient became comatose, a third MRI revealed more extensive DWI restrictions, and he expired despite aggressive care. Autopsy revealed massive brainstem infarcts, a thick lymphoplasmacytic infiltrate, copious Gram-Positive cocci (likely MRSA) and arteries partially occluded with fibrointimal proliferation. This emphasizes the concept that extra-axial DWI restriction can represent pus development in the subarachnoid space – a

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radiographic marker to identify a patient at risk for demise due to septic, meningo-vasculitic infarctions.

Case Report

A 45-year-old right-handed man, with a history of HIV (and a CD4+ T-cell count of 556, not on anti-retroviral medications), presented to our hospital one day after he had noticed the acute onset of horizontal diplopia, weakness of his left face and right (contralateral) arm and leg – hemiparesis alternans. His history, vital signs, and physical exam were otherwise unremarkable. Results of routine laboratory tests were within normal limits. His initial MRI (fig. 1, top) revealed FLAIR signal hyperintensity and restriction on diffusion weighted imaging (DWI) in the left pons, indicative of an acute ischemic stroke that is clinically compatible with the Millard-Gubler syndrome. On this same MRI, but slightly more caudal (fig. 1, bottom), note was made of a subtle, extra-axial, curvilinear, high-signal abnormality on FLAIR, which was also evident on T1, had a high signal intensity on DWI and a matching low signal on apparent diffusion coefficient (ADC) – compatible with diffusion restriction in the subarachnoid space – in the cistern adjacent to the left pons and cerebellum (fig. 1, red arrows). The etiology of this extra-axial, curvilinear entity was unclear at that time. Concurrent MRA was unremarkable.

The patient was admitted to the neuroscience intensive care unit, where cardiac telemetry displayed sinus tachycardia, and transthoracic (followed by transesophageal) echocardiography revealed a normal ejection fraction, valves, and chambers, without clot, vegetation, patent foramen ovale or septal defect. Because of his young age (<55) and lack of 'traditional' stroke risk factors such as hypertension, diabetes, or heart disease, a hypercoagulable serum panel was ordered. It included anticardiolipin antibodies, lupus anticoagulant, protein C and S levels, anti-thrombin III, fibrinogen, factor VIII, prothrombin 20210, homocystine, lipoprotein (a), and sickle cell screen. All of these tests were negative or within normal limits.

During this stroke workup, the patient gradually developed a severe headache, progressing over a few days with meningismus and stupor. Lumbar puncture revealed an opening pressure of 230 mm H_2O, with 250 red blood cells, 75 white blood cells (79% neutrophils), glucose of 80, and protein of 54.

Opportunistic infections such as Cryptococcus, tuberculosis, and syphilis were ruled out, despite low suspicion due to his relatively preserved CD4 count of 556. Acid-fast bacilli test for tuberculosis was negative in his serum and cerebro-spinal fluid (CSF), as was his PPD, and several chest X-rays did not reveal any suspicious lesions, granulomatous or otherwise. The RPR, VDRL, and FTA-ABS tests for syphilis were all non-reactive in his serum and CSF, polymerase chain reaction (PCR) for DNA of Herpes simplex virus 1 and 2, cytomegalovirus and varicella-zoster virus (VZV) were negative in his CSF, and there were no dermatomal vesicles suggestive of VZV anywhere on his body. However, seeping, pustular furuncles, discovered on his knees, were cultured, and grew out methicillin-resistant *Staphylococcus aureus* (MRSA). Blood cultures also became positive for MRSA and intravenous vancomycin was started.

A second MRI of his brain (fig. 2, top) showed extension of intra-axial FLAIR signal hyperintensities with diffusion restriction now seen in the bilateral pons and left cerebellum, indicating both new and exacerbating cerebral infarctions. The more caudal subarachnoid space DWI restriction (fig. 2, bottom) was no longer subtle – increasing in size and expanding more curvilinearly into the left posterior fossa. Communicating hydrocephalus developed, with effacement of the fourth ventricle, dilation of the lateral and third ventricles, and CSF trans-exudation. Another lumbar puncture was performed and it revealed 4 red blood cells, 112 white blood cells (74% neutrophils), glucose of 130, and protein of 2,126. High-dose, broad-spectrum antibiotics (vancomycin, ceftriaxone, and ampicillin) were utilized, along with aggressive intravenous fluids, pressor agents, ventriculostomy, and other supportive care measures. Nevertheless, the patient continued to deteriorate and became comatose. A third and final MRI of his brain was performed (fig. 3) which showed marked diffusion restriction and hyperintense FLAIR signals that had spread from the initial extra-axial area into the brainstem parenchyma, encompassing the entire pons, medulla, and left cerebellum. The repeat MRA revealed irregularity and narrowing of the entire vertebro-basilar circulation, including lack of flow-related enhancement in the left vertebral artery and portions of both posterior cerebral arteries (fig. 4b). The patient soon expired.

At autopsy, the brain weighed 1,212 g. The basilar artery, posterior cerebral arteries and cerebellar arteries were mostly patent on gross examination (fig. 4c) but variable arteritis, thick lymphoplasmocytic infiltration, and partial large- and small-vessel occlusion (due to fibrointimal

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proliferation) were seen on high-power light microscopy (fig. 4d). The basilar meninges were thickened and contained white purulent material (fig. 5) and most of the inferior brainstem and left cerebellum showed recent non-hemorrhagic infarcts. Inflammation and vasculitis also were noted in the cervical spinal cord leptomeninges. Additional gross findings included moderate dilatation of the lateral and third ventricles and aqueduct along with moderate compression of the fourth ventricle. Gram and GMS stains showed copious Gram-Positive cocci (GPC) in chains (fig. 6), most likely the same bacteria – MRSA – that grew in the blood and furuncles. Unlike the GPC in the blood and furuncles, however, the GPC in the brain were not amplifiable for MRSA because there were not enough microorganisms with viable DNA, a common post-mortem phenomenon. Broad-spectrum antibiotic use during hospitalization also probably prevented more precise speciation. Nevertheless, paraffin block extraction and PCR testing at autopsy identified housekeeping genes coding for constitutionally expressed beta-globin cell maintenance proteins.

Discussion

The most likely agent responsible for this patient's bacterial meningo-vasculitis was MRSA, which was cultured directly in his furuncles and blood and was found indirectly in his brain on autopsy (the copious GPC in the leptomeninges were unable to be speciated due to technical reasons). Our theory is that the MRSA likely began as a community-acquired furuncular inoculation, entered the blood stream, spread hematogenously, and then crossed the blood-brain barrier into his subarachnoid space. Our patient's initial presentation, with a mild and classic Millard-Gubler syndrome – hemiparesis alternans – dramatically progressed to stupor and then to coma as a small accumulation of pus in the meningeal space led to a raging, fatal vasculitis with multiple posterior fossa infarctions and resultant hydrocephalus. Our patient's leptomeningeal pathology specimen – packed with a dense, perivascular, lymphoplasmocytic infiltration – supports the notion that the extra-axial, subarachnoid DWI restriction indeed represented the formation of pus. As the pus accumulated, greater areas of restriction were seen on DWI and concomitantly, his brainstem infarctions also extended markedly in size. The pus in his subarachnoid space likely evoked a small-vessel vasculitis at first, and then gradually infarcted larger, more vital areas of his brainstem and cerebellum in a massive large-vessel vertebral-basilar meningo-vasculitis. Cerebral vasculitis of any cause has a predilection for the larger-sized vasculature [4–6] but as seen in figure 4c, on gross examination the patient's basilar artery, posterior cerebral arteries and cerebellar arteries were mostly patent. However, figure 4d shows that on high-power light microscopy, moderate-to-severe fibrointimal proliferation was seen with variable arteritis, partial large-vessel occlusion and subtotal small-vessel occlusion. The devastated posterior fossa contents found on gross autopsy and thick lymphoplasmocytic infiltration on microscopy both support the notion of a severe bacterial, pyogenic process. Vasculitic strokes are rare but occur more frequently in HIV-infected patients [7, 8]. Such individuals may not be able to muster a fever in the acute neuroinfectious setting [7, 8]. Thus, even without elevated temperatures or leukocytosis, and although clear-cut neurologic signs of a classic stroke syndrome can suggest alternate etiologies, such as vertebral dissection, small-vessel lacunar disease, or cardiac embolism – the more likely top-three differential diagnoses in this patient – an infectious vasculitis should still be considered.

Our patient turned out to have a bacterial vasculitis, but viral vasculitides (such as from varicella-zoster or Herpes simplex, for example) may be more commonly suspected, particularly in patients with HIV, which itself could provoke a vasculitis. PCR testing in the CSF for viral agents is helpful but not always 100% sensitive. Our patient's preserved T-cell CD4 count and lack of initial clinical or serologic evidence of sepsis diverted us away from diagnosing bacterial meningovasculitis at first, but the unique presence of restricted diffusion in the adjacent subarachnoid space – and its eventual extension –

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enabled us to postulate that extra-axial diffusion could be a pustular infiltrate. Early consideration of a diagnosis of bacterial vasculitis may benefit patients substantially because rapid administration of therapy (especially with high-dose, broad-spectrum antibiotics) may avert clinical deterioration [10]. However, in our case, aggressive treatment (initiated early) did not prevent his demise. In patients with the most severe immunodepression and much lower CD4 counts than our patient's, even the use of highly active anti-retroviral therapy may not influence the outcome [14].

Community-acquired MRSA has been reported to cause life-threatening, invasive infections, particularly in the brain [9] – but invasive vasculitic MRSA provoking progressive cerebral brainstem infarctions has not, to our knowledge, been documented. We also believe this is the first adult report of extra-axial pus restricting on DWI sequences confirmed by gross and microscopic neuroanatomic dissection. Scant case reports suggest that extra-axial DWI restriction could represent a lymphoma or neurenteric cyst [1, 2]. A case series of MRI findings in acute meningitis in neonates from the Children's Hospital of Philadelphia at the University of Pennsylvania illustrated multiple intra-axial DWI restriction abnormalities in several neonates with meningitis, yet one had an extra-axial restriction, presumably a subdural empyema [3]. The restricted DWI in our case was located in the subarachnoid space of the left cerebellar pontine angle. Clinically and radiographically, this case emphasizes the need to associate extra-axial DWI restriction with pus formation and extension which may be the harbinger for an impending, severe meningo-vasculitis. Even without fever, laboratory markers, or major clinical deficits, patients with this extra-axial DWI restriction can develop fatal large- and small-vessel bacterial meningo-vasculitis and rapidly progressive, recurrent ischemic strokes. Although subtle, as seen in figure 1 in our case, such a DWI restriction must be neuroradiographically entertained as pus. Otherwise, conventional neuroimaging, vital signs, clinical exam, and serologic data may not help identify individuals at risk for vasculitis-induced cerebral ischemia. Immunologically mediated necrotizing vasculitis and thrombosis can manifest as DWI restriction, reflecting local areas of intra-axial ischemia and cytotoxic edema, and are often associated with death or severe neurological deficit [11]. As a result of this case, we contend that extra-axial diffusion restriction can also sprout into a bacterial meningovasculitis causing death or severe neurological deficit. The dense perivascular, lymphoplasmocytic infiltration in our patient's leptomeninges at autopsy support our notion that subarachnoid DWI restriction can accurately represent pus formation. Authors of another series of meningitis patients suggested that cortical fractional anisotropy testing may reveal increased values consistent with adhesion of inflammatory cells and inflammatory activity in the pia-arachnoid space and can be used as a complementary diagnostic tool to identify diffuse meningeal inflammation [12]. Another study revealed significantly higher fractional anisotropy values in 14 neonates with bacterial meningitis before and after receiving antibiotics, demonstrating another use as a noninvasive assessment of meningeal inflammation and treatment response [13]. Certainly more reports, diagnostic modalities, and treatment paradigms are needed to corroborate this rare phenomenon of extra-axial pus formation restricting on DWI, and thereby confirm its role in the development of bacterial meningo-vasculitis and the exacerbation of ischemic stroke.

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Fig. 1. On MRI (top panel), a focal left pontine intra-axial infarct is seen as a high FLAIR signal (left) and DWI restriction (right). Slightly more caudal on this same MRI (bottom panel), there is seen a subtle, extra-axial, curvilinear, FLAIR (upper left) and T1 (upper right) signal abnormality, also showing restricted diffusion with high signal intensity on DWI (lower left) and matching low signal intensity on ADC map (lower right) in the subarachnoid space (red arrows).

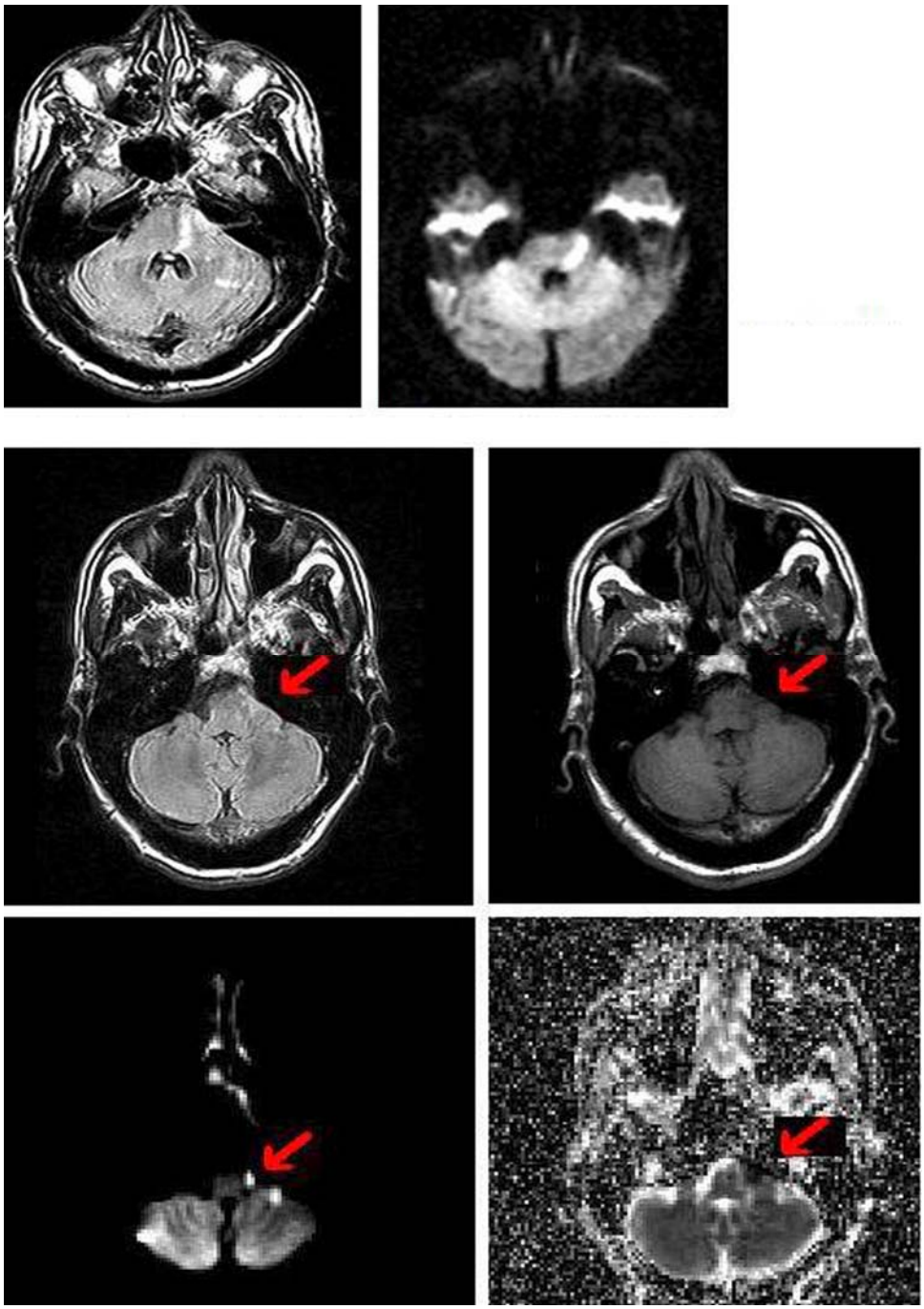

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Fig. 2. Repeat MRI (top panel) revealed fourth ventricle effacement and infarct extension into the brainstem and cerebellum on FLAIR (left) and DWI (right). On this same MRI (bottom panel), the previously subtle cerebello-pontine angle signal has increased in size on FLAIR (upper left), T1 (upper right), DWI (lower left) and ADC (lower right).

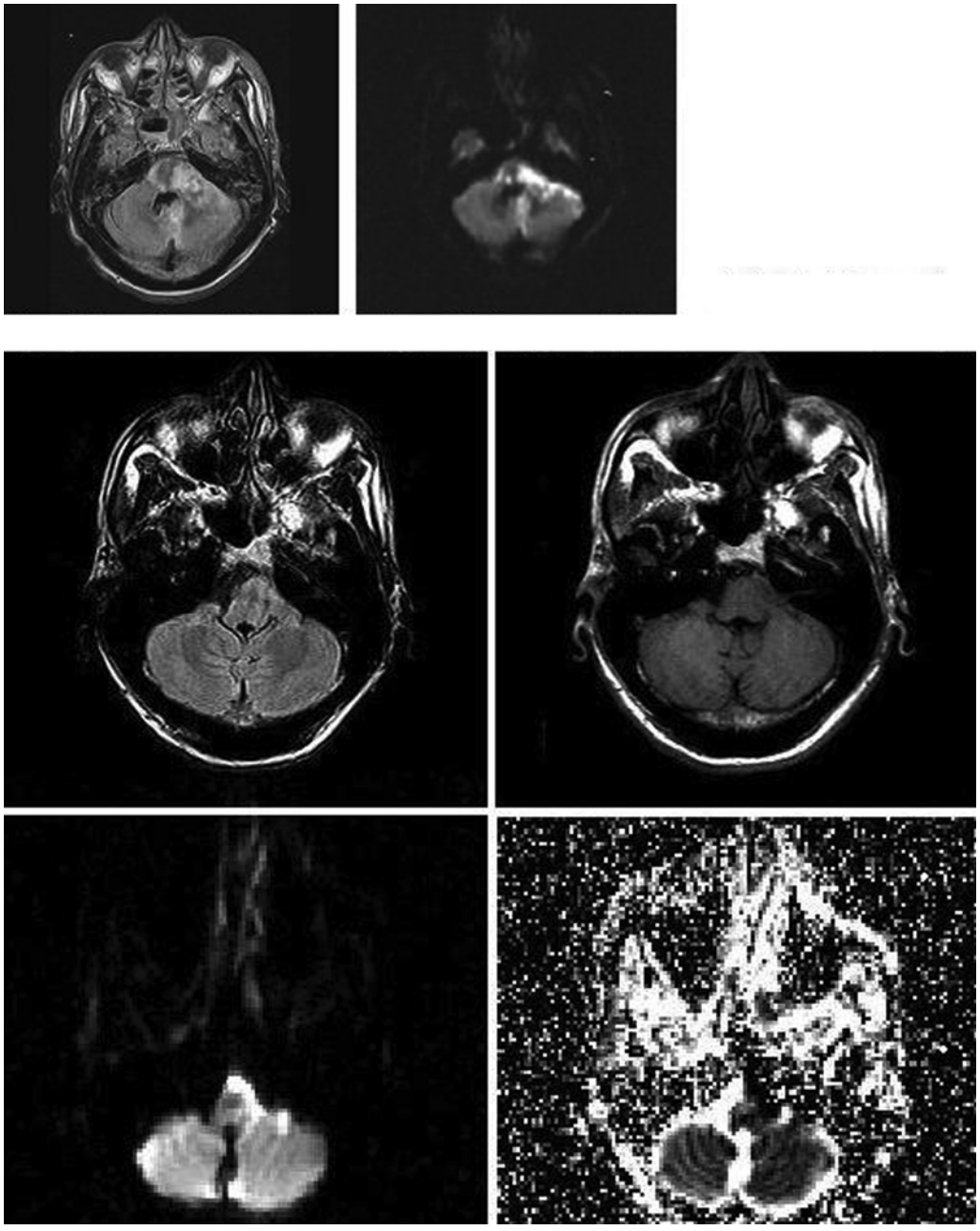

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Fig. 3. A third and final MRI revealed considerable disease progression with marked increase in size of signal abnormalities on FLAIR (upper left) and T1 (upper right) in the brain parenchyma itself. In the subarachnoid space, pons, medulla and cerebellum, the high signal intensities also increased in size on DWI (lower left) with matching low signal intensity on ADC map (lower right). The restricted diffusion in the subarachnoid space represented pus from bacterial meningitis and the restricted diffusion in the brainstem and cerebellum represented acute infarctions.

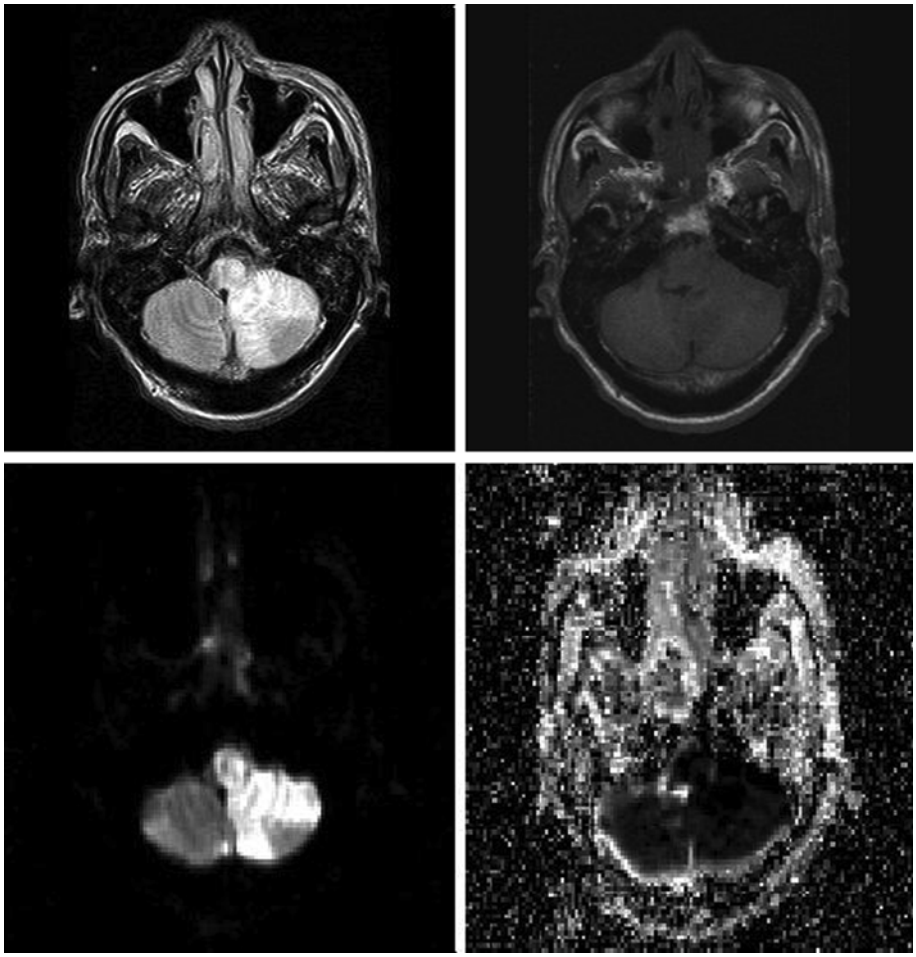

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Fig. 4. MRA initially appeared unremarkable (**a**), but later it appeared vasculitic (**b**) in the basilar and posterior cerebral arteries, with left vertebral artery dropout. Autopsy revealed patency of the basilar, posterior cerebral and cerebellar arteries (**c**) but variable arteritis with partial occlusion by fibrointimal proliferation was seen on high-power light-microscopy (**d**).

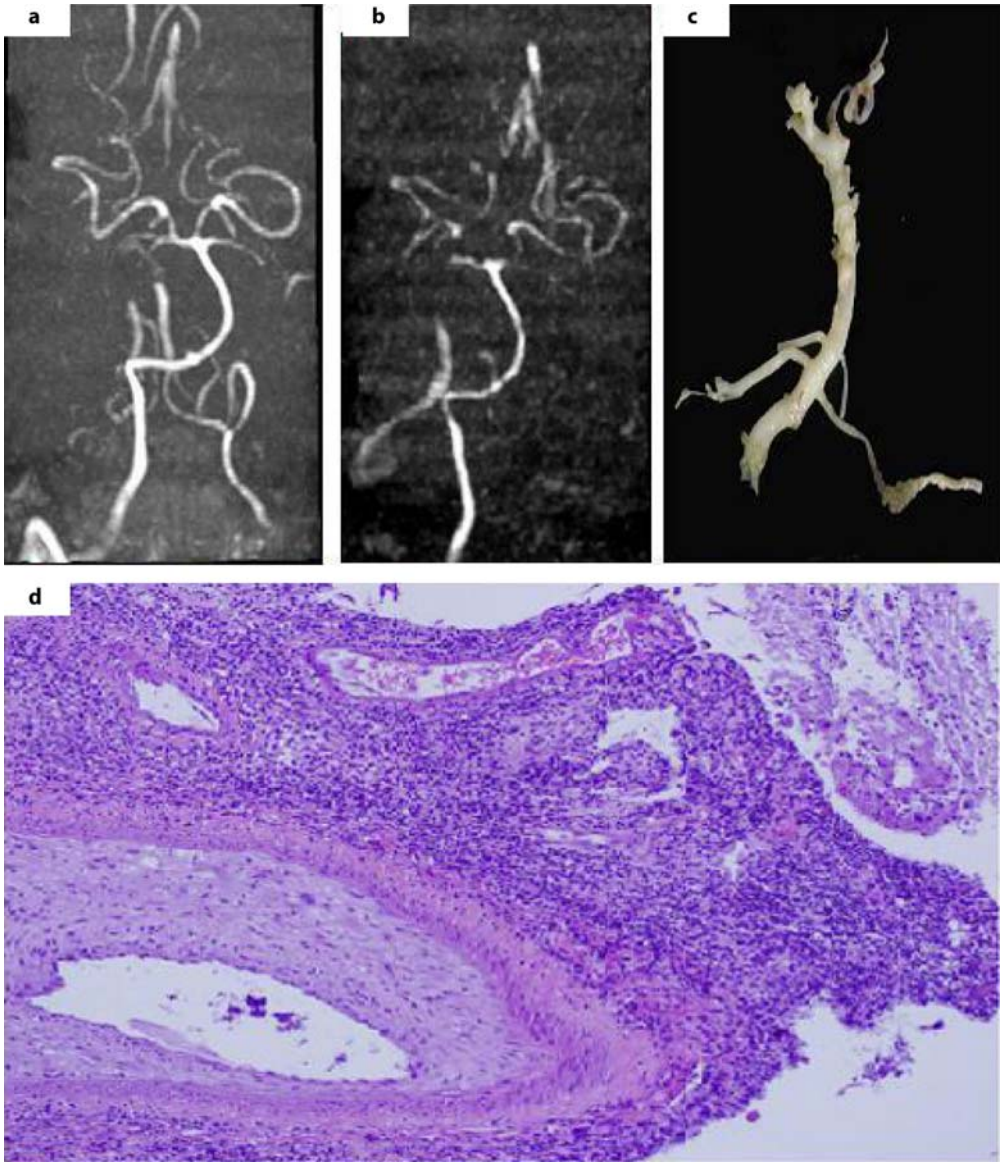

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Fig. 5. Base of brain gross autopsy reveals basilar meningitis that partially obscures pontine circumferential arteries (arrow). Recent, severe necrosis of the left cerebellar hemisphere (star) and pons is seen.

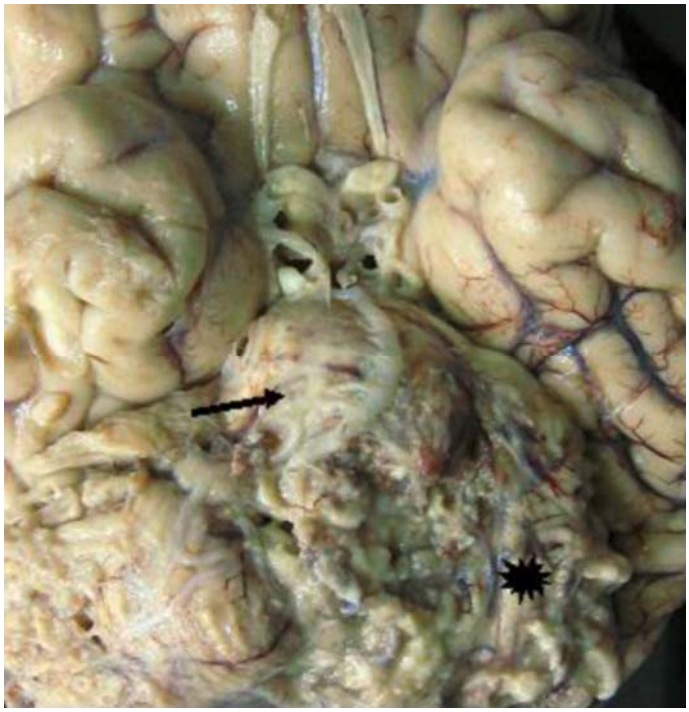
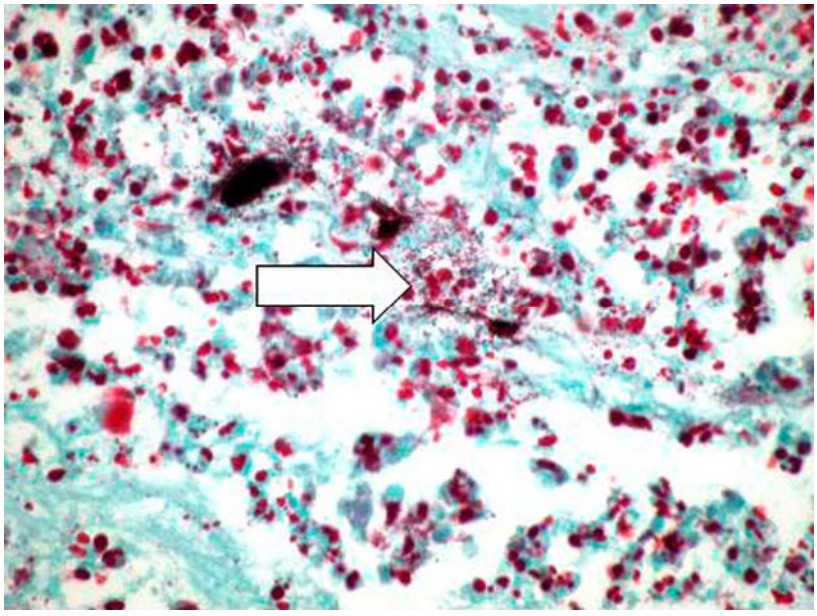


Fig. 6. In the pons, copious Gram-Positive cocci in clusters (arrow), macrophage infiltrates, and capillary proliferation were seen on post-mortem microscopy.



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