Encephalopathy with Staphylococcal Endocarditis: Multiple Neuropathological Findings

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ABSTRACT: *Background:* Infective endocarditis is associated with serious neurological sequelae. *Objective:* Here, we report a patient with *Staphylococcus aureus* endocarditis, secondary to congenital heart disease, with subacute onset of multiple neurological complications. *Results:* Despite prompt antibiotic treatment with rapid sterilization of blood cultures, the patient died with brain herniation within 96 hours of admission. Neuropathological examination showed intraparenchymal hemorrhages, mycotic aneurysms, micro-abscesses and septic arteritis with accompanying infarction. Immunocytochemical studies revealed enhanced CD45 and GFAP immunoreactivity, together with adenosine A1 receptor detection on macrophages and microglia. *Conclusions:* Infective endocarditis is associated with multiple neuropathological lesions, which may contribute to its poor clinical outcome and activation of cells of monocyte-microglial lineage throughout the brain.

RÉSUMÉ: Encéphalopathie accompagnée d'une endocardite staphylococcique: observations neuropathologiques. *Introduction:* L'endocardite infectieuse est associée à des séquelles neurologiques sérieuses. *Objectif:* Nous rapportons le cas d'un patient atteint d'un endocardite à staphyloccoque doré secondaire à une maladie cardiaque congénitale, qui a présenté des complications neurologiques à début subaigu impliquant de multiples hémorragies cérébrales et cérébelleuses. *Résultats:* En dépit d'une antibiothérapie établie promptement et d'une stérilisation des hémocultures, le patient est mort d'une hernie cérébrale, 96 heures après l'admission. L'examen neuropathologique a montré des hémorragies intraparenchymateuses, des anévrismes mycotiques, des micro-abcès et une artérite septique avec infarcissement. Les études immunohistochimiques ont montré une immunoréactivité CD45 et GFAP augmentées ainsi que la détection de récepteurs adénosine A1 sur les macrophages et la microglie. *Conclusions:* L'endocardite infectieuse est associée à des lésions neuropathologiques multiples qui peuvent contribuer à un mauvais pronostic clinique et à l'activation de cellules de la lignée monocytique-microgliale dans tout le cerveau.

Infective endocarditis is frequently accompanied by the development of neurologic disease. As described by Osler[1] in 1885, the classic triad of infective endocarditis includes fever, heart murmur, and hemiplegia. However, several neuropathological lesions may underlie the neurological disease accompanying infective endocarditis, including cerebral mycotic aneurysms, hemorrhage and infarction, micro-abscesses and meningo-encephalitis. Despite the wide use of prophylactic antibiotics and the increasing public and medical awareness, the frequency of neurological complications from infective endocarditis has remained unchanged and is increased in several clinical circumstances including intravenous drug abuse.[2] The most common site of brain injury is usually within the cerebral hemisphere during infective endocarditis, which often becomes manifest within 48 hours of admission in cases of *Staphylococcus aureus*.[3] The mortality accompanying infective endocarditis with neurological complications approaches 80 to 90% in some studies.[4] Intracerebral hemorrhage is an infrequent complication of infective endocarditis (3-8%) but it carries a particularly poor prognosis.[5] Risk factors for intracerebral hemorrhage accompanying infective endocarditis include left-sided heart disease, native valve, mitral regurgitation, and *S. aureus* septicemia. The pathogenic mechanisms underlying intracerebral hemorrhage include hemorrhagic transformation of an infarct and rupture of either a mycotic aneurysm or a vessel

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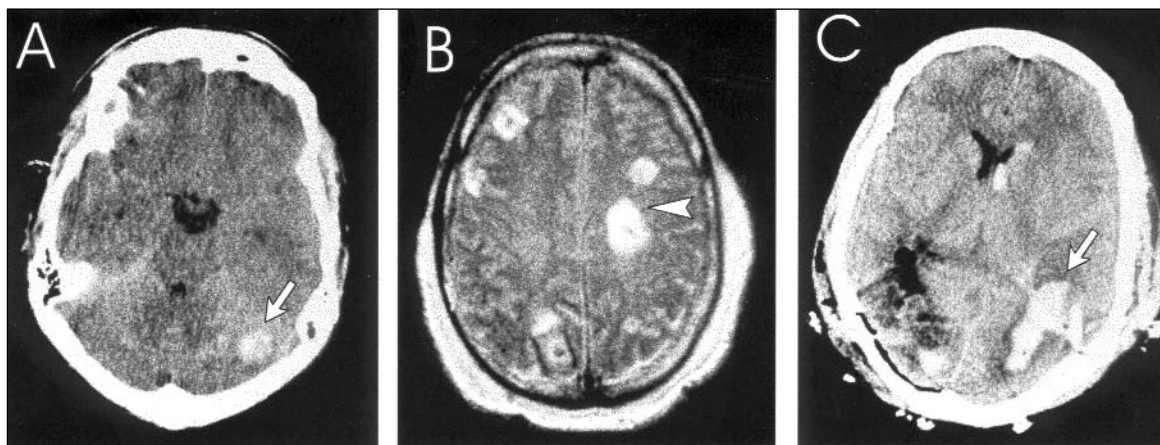
Figure 1: Neuroimaging showing an initial left cerebellar (A) intraparenchymal hemorrhage on CT scan. A subsequent MRI T2 weighted image revealed multiple lesions at day 3 post-admission (B). A CT scan following drain placement showed new hemorrhagic lesions (C).

showing septic arteritis. In the present report, we describe a patient who developed *S. aureus* endocarditis with a bicuspid aortic valve and multiple neuropathological findings accompanied by intense macrophage infiltration.

CASE REPORT

A 35-year-old man was transferred to a tertiary care hospital because of confusion, headache and thrombocytopenia. He presented with a five-day history of fever, headache, and myalgias. Two days prior to admission, visual changes and worsening headache prompted a visit to the local walk-in clinic, a diagnosis of "strep throat" was made and amoxicillin was prescribed. After 24 hours and a negative throat swab, the antibiotic was discontinued. The following evening the patient presented to the nearest emergency department with 'delusional' behavior, staggering gait, fever and headache.

On arrival at the initial hospital, a history revealed migraine headaches, asthma, and a congenital aortic valve abnormality with stenosis. Physical examination was remarkable for a heart rate of 100, temperature of 39.3ºC, a 'peri-oral lesion', and a grade II/VI systolic ejection murmur at the right upper sternal border. The patient's neurologic exam was noted to be normal. Laboratory results revealed a white blood cell count of 7.0, hemoglobin of 143 g/dl, and platelet count of 29,000. Blood cultures were drawn and a lumbar puncture was done at that time, showing the following results: RBC 2130, WBC 350 (90% neutrophils, 10% monocytes), protein 0.75 mg/dl and glucose of 3.1 mg/dl. A cranial CT revealed six discrete intracranial hemorrhages involving both the cerebrum and cerebellum (Figure 1A). The patient was transfused with 6 units of platelets, received intravenous antibiotics: gentamicin, vancomycin and penicillin and was transferred immediately to our hospital under the Neurology service.

Examination on arrival revealed facial and palatine petechiae, neck ecchymosis, a grade II/VI systolic ejection murmur at the aortic region radiating to carotids and precordium, splinter hemorrhages and Janeway lesions. On neurologic examination the patient was oriented to person and place but had slurred speech, left homonymous hemianopsia, right cranial nerve VI palsy, left facial weakness, a left Babinski reflex, left sided motor weakness and neglect.

A transthoracic echocardiogram showed an echobright area near the aortic valve, moderate aortic insufficiency and mitral valve thickening. Blood cultures showed coagulase positive Gram positive cocci, eventually shown to be *S. aureus* at 20 hours, thus prompting an

antibiotic change to cloxacillin. The patient improved neurologically over 36 hours and his platelet count normalized. Acute neurological deterioration developed on day three following admission, with an unresponsive right pupil, papilloedema, bilateral cranial nerve VI palsies, bilateral positive Babinski reflexes and decerebrate posturing on the right. CT scan revealed a large left hemisphere hemorrhage and obliteration of basal cisterns.

The patient was taken to the operating room for emergent craniotomy and drainage. Post-op day one the patient demonstrated remarkable neurological improvement. A magnetic resonance angiogram did not exhibit any vascular structural abnormalities but a MRI showed multiple hemorrhages (Figure 1B). Postoperatively on day two, after continued improvement the patient acutely deteriorated with a rapid drop in blood pressure and was unresponsive neurologically. A head CT showed a repeat hemorrhage into areas previously drained (Figure 1C). The patient was pronounced brain-dead, based on clinical findings and absent blood flow on perfusion scan.

PATHOLOGICAL FINDINGS

Autopsy was limited to the brain and heart, revealing a congenitally abnormal heart with bicuspid aortic valve and vegetations, accompanied by gram-positive cocci. Erosion into the myocardium had occurred, with necrosis and purulent material, resulting in a ring abscess, exhibiting gram-positive cocci. Multiple myocardial infarcts of varying age were present.

Neuropathological autopsy showed an edematous brain weighing 1500 grams. Subarachnoid blood was present, accompanied by obvious hemorrhages in the left occipital and left cerebellar hemispheres and herniation of the cerebellar tonsils. Histological staining revealed microscopic areas of septic arteritis and necrotic infarction (Figure 2A) and multiple micro-abscesses (Figure 2B) throughout the cerebral hemispheres involving the cerebral cortex and white matter. Intense microglial activation and monocyte infiltration (Figure 2B), together with a few neutrophils, were observed throughout the neuropil but was most striking in the vicinity of hemorrhages. Secondary midbrain tegmental (Duret) hemorrhages were also present together with hemispheric hemorrhages. Several mycotic aneurysms were identified (Figure 2C), and at least two
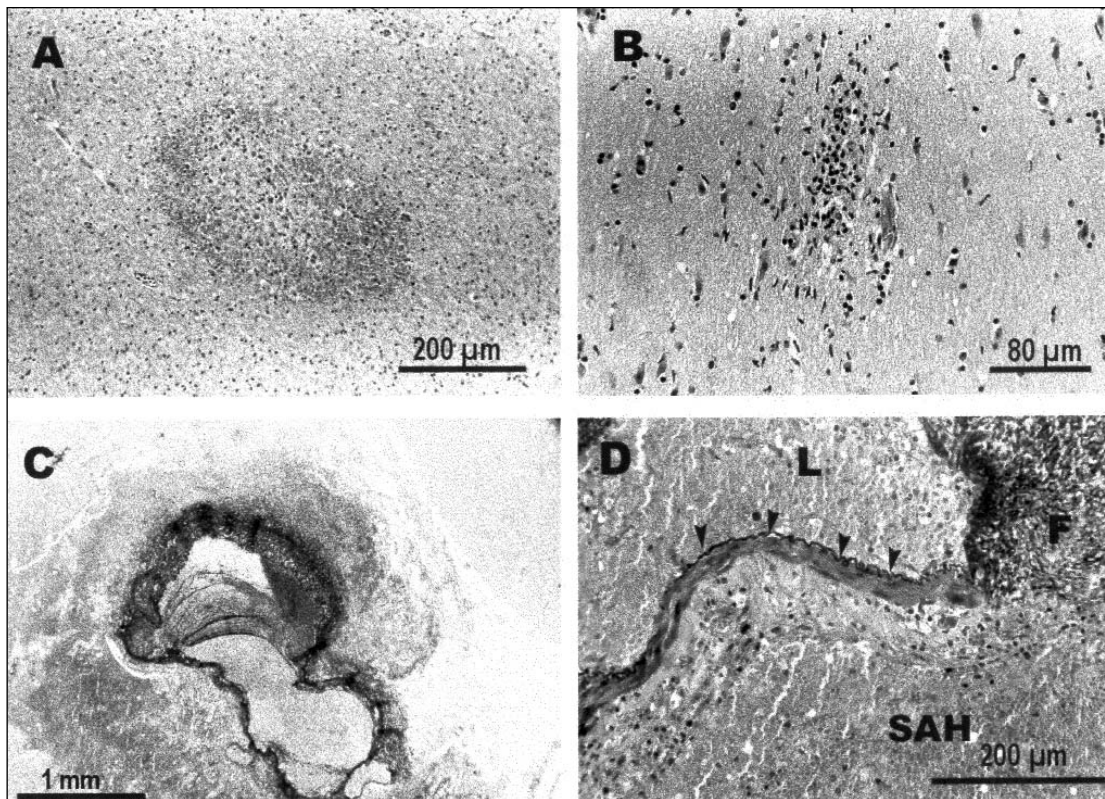
Figure 2: Neuropathological studies of 8 μm paraffin embedded sections revealed several distinct features. Geographically demarcated microinfarcts secondary to septic arteritis, which measured several hundred μm in diameter (A). Micro-abscesses in cerebral parenchyma consisted of microglial nodules 50-100 μm across (B), as have been described in septic encephalopathy. Several mycotic aneurysms measured 1-2 mm in diameter (C). Close examination (D) revealed destruction of the wall of the artery, seen as a sudden disappearance of normal arterial structure including internal elastic lamina (arrowheads). The lumen (L) and the subarachnoid hemorrhage (SAH) are separated at the upper right of the photomicrograph by dark fibrin (F).

aneurysms had ruptured secondary to damage of the internal elastic lamina (Figure 2D).

Immunohistochemical studies[6] revealed marked microglial activation with both ramified and ameboid (Figure 3A, arrows) microglia that were CD45 immunopositive (Zymed Lab., San Francisco, CA) and increased in number and size (Figure 3A). Similarly, astrogliosis, indicated by glial fibrillary acid proteins (GFAP) immunoreactivity (Dako, Carpentier CA) was prominent and remote to the actual sites of the hemorrhage (Figure 3B). Glial cells resembling microglia were immunopositive for the adenosine A1 receptor (A1AR) (Alpha Diagnostic International, San Antonio, TX) and were abundant (arrowheads) throughout the white matter of the brain in the neuropil and perivascular regions (Figure 3C). These latter glial cells were double-immunopositive for CD45 (arrows-brown) and A1AR (arrowhead-black) (Figure 3D).

DISCUSSION

This report describes a fatal outcome associated with staphylococcal endocarditis, underscoring the need for vigilance in assessing patients with congenital heart disease who present with nonspecific symptoms at the onset of their disease. In addition to the diversity of clinical and radiological findings accompanying endocarditis in this patient, multiple neuropathological lesions were observed in the brain including (a) ruptured mycotic aneurysms, (b) intracerebral hemorrhage, (c) multiple micro-abscesses and (d) areas of infarction secondary to septic arteritis, together with diffuse activation of cells of monocyte-microglial lineage throughout the brain. Finally, this is the first description of A1AR expression on glia in the context of an acute inflammatory CNS disease.

Central nervous system symptoms and complications of bacterial endocarditis are common, occurring in 20-40 % of all patients with infective endocarditis and may be presenting symptoms in 12-23% of cases.[7] The present case is novel in several aspects including the development of cerebellar hemorrhages, a comparatively rare complication that likely contributed to the patient's death via tonsillar herniation.[8,9] In addition, this patient responded rapidly to systemic antibiotics with clearance of the bacteremia, yet neurological deterioration and death still occurred, suggesting that the pathogenesis of the neurological disease is not dependent on ongoing septicemia but rather on other components of the neuropathology. Diverse
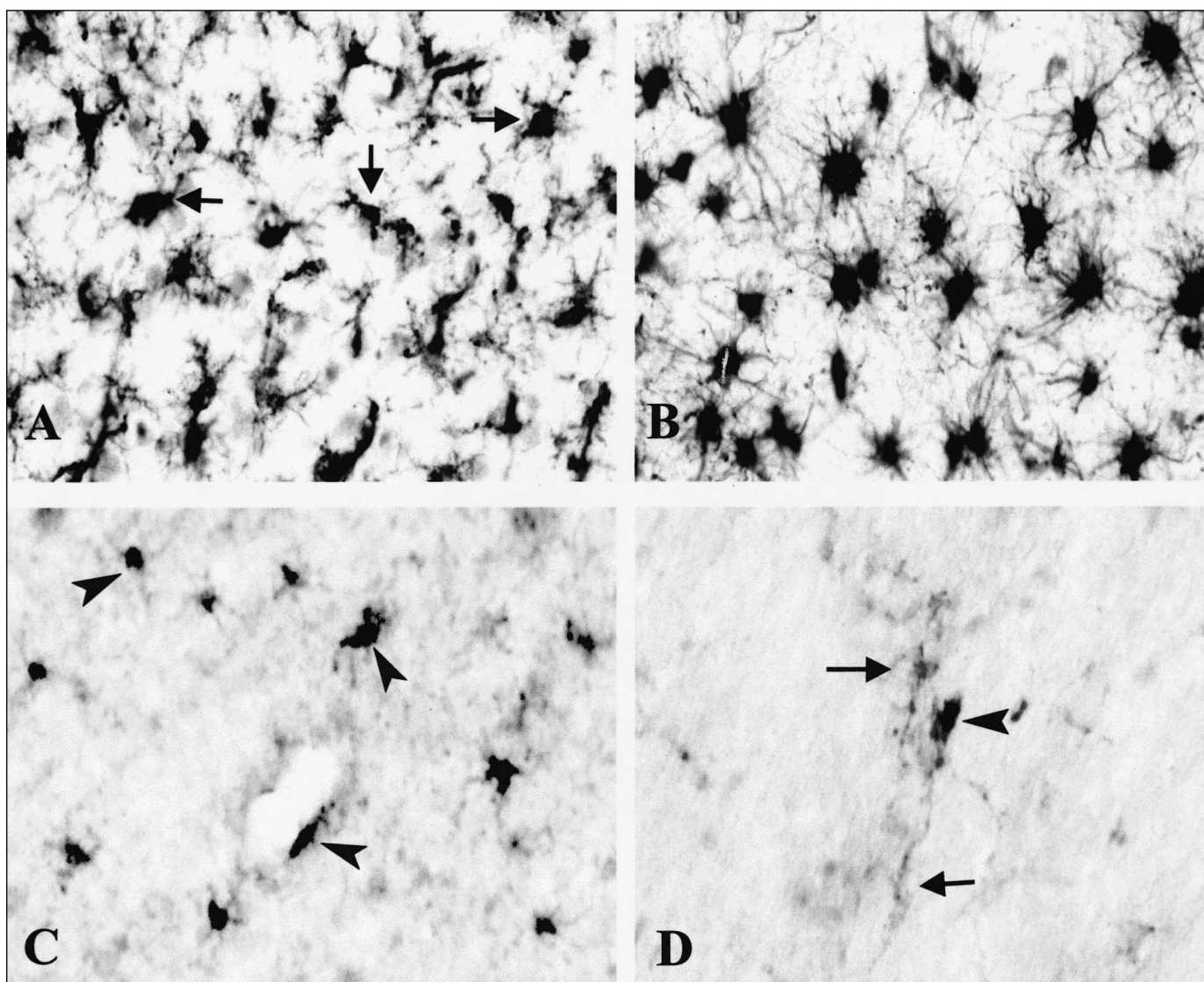
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Figure 3: *Immunohistochemical studies of 40 µm free-floating brain sections remote to hemorrhagic lesions exhibited increased CD45 (arrow) immunoreactivity on amoeboid and ramified microglia (A), increased GFAP immunoreactivity on hypertrophied astrocytes (B), adenosine A1 receptor (A1AR) expression on parenchymal and perivascular glia, resembling microglia (arrowhead) (C) and glial cells that were double immunopositive for CD45 (brown) and A1AR (black) (D).*

neuropathological findings in the brain included mycotic aneurysms and septic arteritis, resulting in intracerebral hemorrhage. Intense activation of cells of monocyte-macrophage lineage was also apparent and could be attributed to one or several of the observed neuropathological lesions, in part due to ischemia.[10] Activation of cells of monocyte-microglial lineage may result in the expression of potentially pathogenic molecules including proinflammatory cytokines such as TNF-α[11] or alternatively, enzymes such as matrix metalloproteinases[12] that alter blood-brain barrier function or degrade the extracellular matrix together. This may be indicated by enhanced expression of the acid phosphotase, CD45, which is associated with immune activation.[13]

The extent of monocyte-microglial activation was significant in the present case and likely involved several different cell types including activated microglia as well as differentiated monocyte-derived macrophages, based on the immunocytochemical findings including adenosine A1 receptor immunoreactivity. Although adenosine receptors are usually regarded as neuronal proteins, the increased expression of the adenosine receptors on activated microglia may provide a therapeutic opportunity in disease characterized by microglial activation. Adenosine receptors are widely recognized as potent regulators of cytokine and MMP[14] expression and recent studies indicate that adenosine A1 receptor specific agonists are effective *in vivo*.[15] Thus, concurrent neuroprotective strategies may be feasible in the treatment of

infectious and inflammatory brain diseases associated with microglial-macrophage activation such as intracerebral hemorrhage, multiple sclerosis, and HIV-associated dementia.

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