Case Records of the Massachusetts General Hospital

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

Case 9-2002

PRESENTATION OF CASE

An 80-year-old woman was admitted to the hospital because of sudden unilateral blindness.

The patient had a long history of medical problems. These included hypertension; mitral and tricuspid regurgitation, which had been treated by valvuloplasties; atrial fibrillation, for which she was taking warfarin; right-sided congestive heart failure; peripheral vascular disease; and chronic renal insufficiency, with a base-line creatinine level as high as 2.4 mg per deciliter (212 μmol per liter). Chronic pancytopenia was ascribed to congestive splenomegaly with hypersplenism. She had undergone a left carotid endarterectomy one year before admission.

Twenty-two days before the admission under discussion, the patient underwent an elective open cholecystectomy because of symptomatic cholelithiasis; a splenectomy was performed during the same operation because of an increasing requirement for blood transfusion and the possibility that splenomegaly was a factor in her anemia. Gross examination revealed congestion and moderate enlargement of the spleen, which weighed 420 g. Microscopical examination showed congestion and occasional foci of extramedullary hematopoiesis. Examination of several lymph nodes at the splenic hilus disclosed hemosiderosis. The postoperative course was uncomplicated except for epistaxis while the patient was receiving heparin. The epistaxis was treated with nasal packing. On the 15th hospital day, the patient was transferred to a rehabilitation hospital, where her temperature ranged as high as 37.2°C.

Six days before the admission under discussion, the patient had a headache with severe pain in the left eye, which gradually worsened. Three days later, examination in the emergency ward of this hospital showed evidence of preseptal cellulitis of the left eye (i.e., cellulitis anterior to the fibrous septum of the left orbit), with extension across the nasal bridge to the right infraorbital area. No visual problems or limitation of extraocular movement was evident. Laboratory studies were performed (Table 1). A cranial computed tomographic scan obtained without the administration of contrast material and a magnetic resonance imaging (MRI) scan showed normal-appearing sinuses and orbits, except for the presence of a retention cyst in the right sphenoid sinus. Nafcillin was prescribed, and the patient returned to the rehabilitation hospital.

The following day, the headache had improved; treatment with cefazolin was begun. The next day (the day before the current admission), the left eyelid was swollen shut. The day of admission, the patient had sudden complete blindness in the left eye and diminished vision in the right eye, with severe bilateral eye pain and headache. She was readmitted to this hospital.

TABLE 1. BLOOD CHEMICAL AND ENZYME VALUES.*

VARIABLE	3 DAYS BEFORE ADMISSION	ON ADMISSION	2ND HOSPITAL DAY	3RD HOSPITAL DAY
Urea nitrogen (mg/dl)	77	80	76	85
Creatinine (mg/dl)	1.9	2.1	1.9	2.3
Glucose (mg/dl)	193	140		
Calcium (mg/dl)				8.3
Phosphorus (mg/dl)				6.9
Sodium (mmol/liter)	130	132	132	132
Potassium (mmol/liter)	4.6	4.9	3.7	3.5
Chloride (mmol/liter)	94	89	90	89
Carbon dioxide (mmol/liter)	28.6	28.4	27.5	27.6
Magnesium		Normal		
Osmolality (mOsm/kg of water)		291	298	
Lactate dehydrogenase (U/liter)		3301		
Aspartate aminotransferase (U/liter)		132		
Alkaline phosphatase		Normal		
Creatine kinase		Normal		
Creatine kinase MB		Normal		

*To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the value for calcium to millimoles per liter, multiply by 0.250. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229.

The temperature was 37.2°C, the pulse was 90, and the respirations were 20. The blood pressure was 170/75 mm Hg.

The patient was cachectic. Examination revealed improvement in the preseptal cellulitis. There was complete loss of light perception in the left eye, with occlusion of the central retinal artery, and swelling of the optic disk suggesting ischemia of the optic-nerve head. Motility was severely decreased in all directions, and there was complete ptosis. The visual acuity in the right eye was 20/400. Although there were crusts of old blood and nasal packs on the turbinate bones on both sides, the underlying mucosa appeared normal. The heart was enlarged; the rhythm was irregular, and there was a grade 2 holosystolic murmur. The lungs were clear.

Laboratory studies were performed (Tables 1 and 2). An electrocardiogram showed atrial fibrillation with a ventricular rate of 78 beats per minute, right bundle-branch block, and ectopic ventricular beats. A chest radiograph disclosed cardiomegaly and interstitial pulmonary edema. An MRI study of the brain, performed after the administration of gadolinium, showed thickening of the mucosa of the left maxillary, sphenoid, and ethmoid sinuses; a retention cyst in the right sphenoid sinus; and smooth, mild dural enhancement that was present bilaterally but more extensive on the left side. There was enhancement indicative of preseptal and nasal soft-tissue swelling on both sides. The superior ophthalmic veins appeared normal, and there was no evidence of cavernous sinus thrombosis.

Specimens of blood were drawn for culture. Treatment with nafcillin was continued, and ceftriaxone, metronidazole, furosemide, lisinopril, spironolactone, hydrochlorothiazide, ranitidine, digoxin, heparin, acetaminophen, and morphine were administered.

On the second hospital day, the temperature was 37.3°C. There was swelling of both optic nerves. A specimen of tissue overlying a turbinate bone and a specimen of the left temporal artery were obtained by biopsy. High-dose methylprednisolone was administered. Laboratory tests were performed (Tables 1 and 2). Tests for antinuclear antibodies and rheumatoid factor were negative. Microscopical examination of a wet preparation from a nasal swab was negative for fungi.

A cranial MRI scan (Fig. 1) showed abnormal enhancement of the orbital contents; the enhancement was greater on the left side than on the right. The swelling, edema, and enhancement of the preseptal soft tissue on the left side persisted. There was per-

TABLE 2. HEMATOLOGIC LABORATORY VALUES.*

VARIABLE	ON ADMISSION	2ND HOSPITAL DAY	3RD HOSPITAL DAY
Hematocrit (%)	27.1	23.6	25.3
Mean corpuscular volume (μm^3)	92		
Erythrocyte sedimentation rate (mm/hr)	129		
Reticulocyte count (%)	5.1		
White-cell count (per mm^3)	20,400	17,800	23,700
Differential count (%)			
Neutrophils	86	86	
Lymphocytes	2		
Monocytes	11		
Eosinophils	1		
Platelet count (per mm^3)	207,000	235,000	280,000
Prothrombin time (sec)	16.8†		
Partial-thromboplastin time (sec)	Normal	43.2	
Iron (μg/dl)		64	Normal
Iron-binding capacity (μg/dl)		172	
Ferritin (ng/ml)		2,911	
Folic acid			Normal

*To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

†The control value was 12.4 seconds.

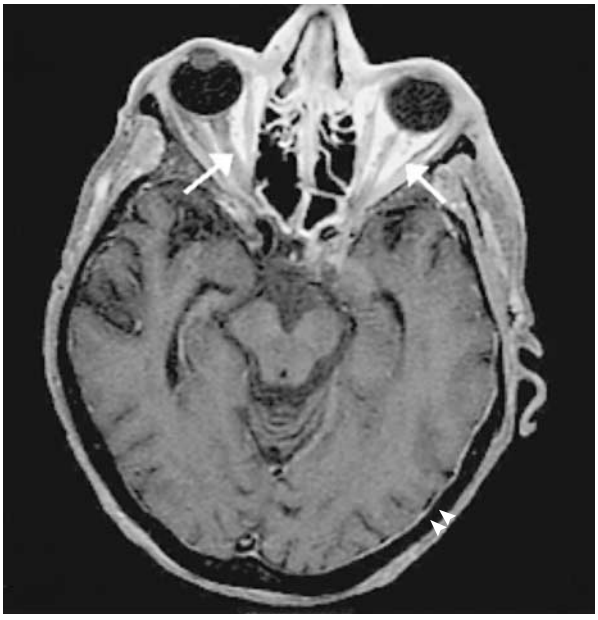

Figure 1. Axial, Fat-Saturated, T_1-Weighted MRI Scan of the Orbits, Obtained after the Intravenous Administration of Gadolinium, on the Second Hospital Day.

The preseptal and nasal subcutaneous soft tissues are thickened. The mucosa of the sphenoid and ethmoid sinuses is thickened and enhanced. The retro-orbital fat is extensively infiltrated, with abnormal enhancing tissue on both sides (arrows). The dura is also thickened and enhanced, especially on the left side of the head (arrowheads).

TABLE 3. FINDINGS ON LUMBAR PUNCTURE ON THE THIRD HOSPITAL DAY.

VARIABLE	FINDING
Initial pressure (mm of water)	320
Appearance of fluid	Clear, colorless
Glucose (mg/dl)	104*
Protein (mg/dl)	24
Lactate dehydrogenase (U/liter)	33
Cells	Absent

*The semiquantitative glucose level in a finger-stick specimen obtained at the same time was 235 mg per deciliter. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

sistent opacification of the right sphenoid and thickening of the mucosa of the sphenoid, ethmoid, and frontal sinuses bilaterally and of the left maxillary sinus, with enhancement on high-signal T_1-weighted and T_2-weighted images. There was bilateral enhancement of the dura, most prominently in the left frontal area. The major vascular flow voids were patent.

On the third hospital day, the temperature was 36.7°C. The patient had increased pain around the right eye and pain on the right side of the forehead. Ocular examination revealed occlusion of both central retinal arteries and bilateral optic-nerve swelling, as well as a venous occlusion in the left eye. The motility of the right eye was unchanged except for a new, partial third-nerve palsy. Laboratory tests were performed (Tables 1 and 2). Three blood-culture specimens were sterile. A lumbar puncture was performed (Table 3).

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. DON C. BIENFANG*: May we review the pertinent radiographic images?

DR. BRADLEY R. BUCHBINDER: An axial, contrast-enhanced, fat-saturated, T_1-weighted MRI study of the brain and orbits, performed on the second hospital day (Fig. 1), shows thickening of the preseptal and nasal subcutaneous soft tissues. There is mucoperiosteal enhancement of the sphenoid and ethmoid sinuses; extensive, abnormal enhancement within the orbits, which is greater on the left side than on the right; and dural enhancement, which is more prominent on the left side.

*Chief, Neuro-Ophthalmology, Brigham and Women's Hospital; assistant professor of ophthalmology and neurology, Harvard Medical School — both in Boston.

DR. BIENFANG: This elderly woman, who had multiple medical problems, was admitted to the hospital because of sudden, unilateral loss of vision after a six-day illness that began with cellulitis involving the left eye. The process spread rapidly to the paranasal sinuses and both eyes, with involvement of the extraocular muscles. A prominent feature of the disease process was evidence of occlusion of both central retinal arteries and at least one vein.

Diagnostic considerations in this case are listed in Table 4. When one encounters a patient with rapid development of ocular arterial disease, giant-cell arteritis (also called temporal arteritis) immediately enters the differential diagnosis, as it did in this case. High-dose methylprednisolone was administered while the patient's physicians were awaiting the results of a temporal-artery biopsy. Despite this appropriate treatment, the ocular disease progressed, and unlike giant-cell arteritis, it involved not only arteries but also a vein and the paranasal sinuses.

Could the orbits have become so packed with a space-occupying lesion that their vessels were severely compressed, resulting in ischemic changes? That sequence of events is possible, but the orbital vessels are very resistant to compression by surrounding abnormal tissue, making a malignant tumor or an orbital pseudotumor improbable. In addition, the very rapid progression of the disease is not characteristic of such lesions, and an orbital pseudotumor is typically unilateral.

In Wegener's granulomatosis, there may be mass lesions and involvement of the blood vessels, and this disease has been reported in the orbit. However, imaging of the sinuses typically shows more extensive disease than that seen in this case, and there is no other evidence of Wegener's granulomatosis.

Infection

Elimination of these categories of disease leaves infection as the probable cause of the patient's illness. Bacterial infection (bacterial orbital cellulitis) is possible but unlikely in view of the extensive vessel involvement. The leading diagnostic consideration is mucormycosis, which is commonly associated with marked vascular involvement and occlusion. Mucormycosis is typically seen in debilitated patients, patients with diabetic ketoacidosis,[1] and patients who are severely immunosuppressed.[2-4] Leukemia and dialysis have also been reported to predispose patients to this infection.[5,6] Recently, cases of rhino-orbital mucormycosis have been described in patients with iron overload, which this woman had, as evidenced by her very high ferritin level. In the reported cases, however, the patients had received the iron-chelating agent deferoxamine.[2,7-11] Did this patient receive that drug?

TABLE 4. DIAGNOSTIC CONSIDERATIONS IN THE CURRENT CASE.

Giant-cell arteritis (temporal arteritis)
Malignant tumor
Orbital pseudotumor
Wegener's granulomatosis
Bacterial orbital cellulitis
Mucormycosis

DR. DIANE KARLUK (Neuropathology): No, she did not.

DR. BIENFANG: It is still uncertain whether untreated iron overload can predispose a person to mucormycosis. In one reported case,[2] a patient with hemochromatosis had rhinocerebral mucormycosis due to infection with organisms of the genus cunninghamella rather than of the more commonly involved genus, mucor.

Other Aspects of the Case

Since the diagnostic focus in this case is on the patient's orbital disease, scanty information about her other illnesses is given in the case record. Although she is described as having had pancytopenia, the cytopenia during her present illness was largely confined to her red cells. In the absence of evidence of blood loss, I assume that the anemia was hemolytic. It was ascribed to hypersplenism, but it persisted despite splenectomy and transfusions. Her splenic congestion may have been due to portal hypertension, but we are not told of any other manifestations of that disorder.

Diagnostic Procedure

The diagnostic procedure was apparently not the temporal-artery biopsy or the biopsy of tissue overlying a turbinate bone. I assume that the former was negative for giant-cell arteritis and that the results of the latter were insufficient to establish a diagnosis. It is likely that more tissue was obtained from the nose, sinuses, or orbit and that examination revealed mucormycosis.

A PHYSICIAN: How do you interpret the thickening and enhancement of the dura?

DR. BIENFANG: Nodular thickening and enhancement are pathologic findings, but smooth, diffuse enhancement of the dura is nonspecific. However, it may be related to spread of the infection to the cerebral meninges.

DR. DAVID E. TOKER (Neurology): Because of the sudden unilateral loss of vision, which was accompanied by a high erythrocyte sedimentation rate and anemia, we initially considered the possibility of giant-cell arteritis, particularly after the biopsy specimen of tissue overlying the turbinate was reported to be negative for giant-cell arteritis. Corticosteroid therapy was administered for 24 hours, but the patient did not have the dramatic response that is typical of giant-cell arteritis, and her ocular disease was progressing. At that point, we ordered more biopsies and began the intravenous administration of high-dose amphotericin B in anticipation of a diagnosis of mucormycosis.

CLINICAL DIAGNOSIS

Invasive mucormycosis of the orbits and sinuses.

DR. DON C. BIENFANG'S DIAGNOSES

Rhino-orbital mucormycosis, fulminant, probably due to the genus mucor, of the class Zygomycetes.

Tissue iron overload.

PATHOLOGICAL DISCUSSION

DR. KARLUK: We obtained biopsy specimens from the sphenoid and ethmoid sinuses, as well as from the orbital foramen, the optic-nerve sheath, and the apical fat of the orbit. Examination of specimens of the mucosa of the left ethmoid sinus (Fig. 2, 3, and 4) and of a nasal turbinate showed many blood vessels filled with thrombi that contained broad, nonseptate hyphae with right-angle branches — characteristics of fungi of the order Mucorales. Silver staining showed fungal hyphae invading the vessel walls (Fig. 5). The diagnosis was angioinvasive mucormycosis.

DR. TOKER: For the next two days, the disease seemed to stop progressing, but then it worsened. We instituted hyperbaric-oxygen treatment, which initially appeared to be beneficial, but the patient could not tolerate it because of claustrophobia. The addition of fluconazole and rifampin to the antibiotic regimen was followed by partial clinical resolution of the orbital disease. At that point, intercurrent renal failure, presumably associated with the use of amphotericin B, led to deterioration of her condition, and further treatment was limited to comfort measures.

DR. KARLUK: The patient died five weeks after admission. The autopsy was limited to the brain. Microscopical examination of the cavernous sinuses revealed invasion of the internal carotid arteries by fungal hyphae morphologically identical to those seen in the biopsy specimens obtained before the patient died. Both arteries had irregular walls that were thickened by inflammatory-cell infiltration and fibrosis. Cranial-nerve fibers coursing through the cavernous sinuses and the base of the skull showed patchy inflammation and degeneration consistent with ischemic injury. Fungal hyphae were present in the dura at the base of the skull and in the mucosa of the left ethmoid sinus.

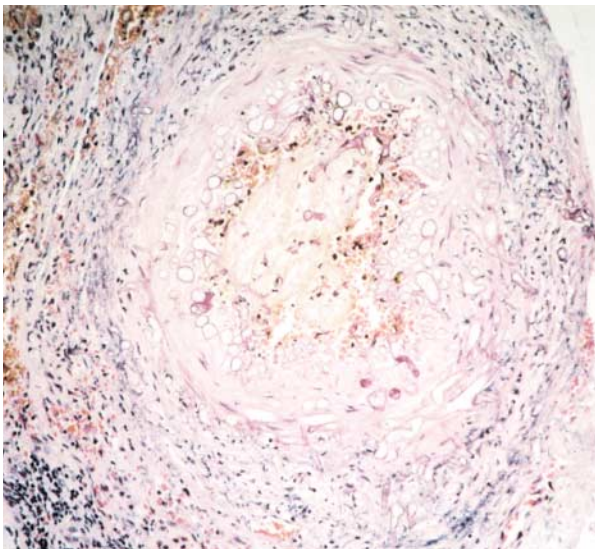

Figure 2. Thrombosed Vessel from the Mucosa of the Ethmoid Sinus (Hematoxylin and Eosin, ×130).

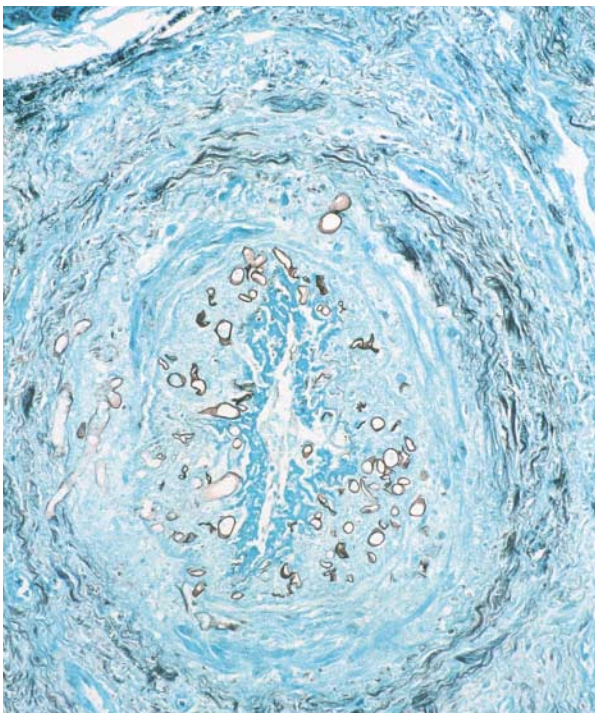

Figure 3. Fungal Hyphae within the Wall of the Vessel Shown in Figure 2 (Silver Stain, ×130).

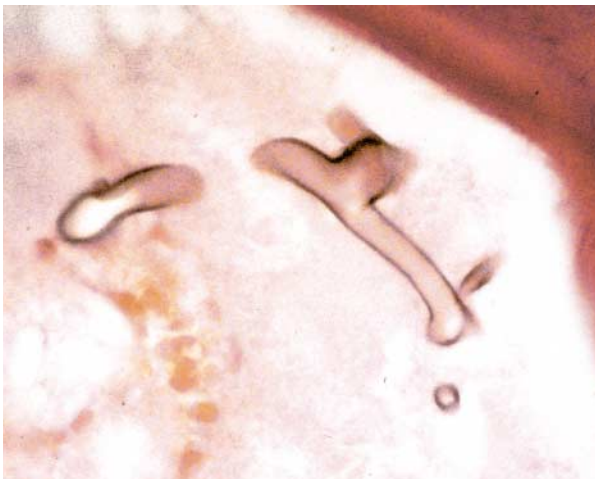

Figure 4. Fungal Hyphae with Right-Angle Branching (Hematoxylin and Eosin, ×600).

Sectioning of the cerebral hemispheres revealed small foci of brown discoloration and tissue loss in the subcortical white matter of the left fronto-orbital gyri and in the right and left centra semiovale. Microscopical examination revealed areas filled with macrophages, a finding consistent with recent infarcts. Since fungi were not identified within adjacent meningeal or penetrating cortical vessels, the infarcts may have been due to unidentified thromboembolism of inflammatory tissue originating in the internal carotid arteries.

Clinical subtypes of mucormycosis include rhino-orbito-cerebral, pulmonary, gastrointestinal, disseminated, and cutaneous forms.[12] The rhino-orbito-cerebral form is the most common subtype and is associated with the highest mortality rate.[13,14] In the current case, the morphologic features of the organism are consistent with organisms of the order Mucorales, but cultures for such organisms were negative.

Mucorales fungi are found in the air, in bread and fruit molds, in soil, and in decaying plant and animal matter.[12] Their rapid growth and prolific spore-forming capability lead to their ubiquitous dissemination in the environment. Rhino-orbito-cerebral infection begins when spores are inhaled and alight on the turbinate bones. Infection proceeds by direct extension or hematogenous spread to the sinuses and orbits.

A PHYSICIAN: Was surgical treatment considered in this case?

DR. MARLENE L. DURAND (Infectious Diseases): Débridement is an essential part of therapy for mucormycosis in nearly all cases but was not indicated in this elderly, debilitated patient who had clinical evidence of cavernous-sinus involvement very early

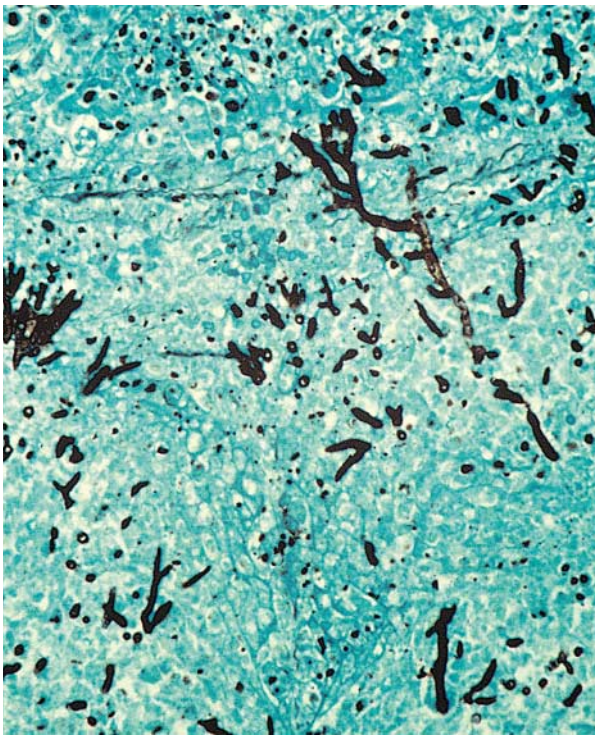

Figure 5. Numerous Black Fungal Hyphae within the Lumen of the Right Internal Carotid Artery (Silver Stain, ×400).

in the course of her disease. An extraordinary feature of this case was that endoscopic examination of the sinuses and nasal passages showed no abnormalities instead of revealing necrosis, which one would expect with mucormycosis.

DR. TOKER: After antibiotic therapy was administered, there was definite improvement in extraocular-muscle function. Is there an explanation for that?

DR. E. TESSA HEDLEY-WHYTE (Neuropathology): Some of the damage to the nerves involved in the disease process was caused by edema rather than infarction. The edema may have interfered with conduction and then regressed to some extent after treatment, allowing partial recovery of muscle function.

DR. ROBERT E. SCULLY (Pathology): As Dr. Bienfang stated, we included in the case record only scanty data concerning this patient's complex hematologic disorder. The hematologists believed that the anemia may have been caused by multiple factors, including hypersplenism with sequestration of the blood components, azotemia, and the previous valvuloplasties, but they were uncertain of the relative contribution of each of these putative causes. The valvuloplasties were considered to have a role in the anemia, since it became much worse after the mitral valvuloplasty, and occasional schistocytes were found in the peripheral blood.

ANATOMICAL DIAGNOSIS

Mucormycosis, rhino-orbital.

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