The Coexistence of Acute Rheumatic Fever and Sickle Cell-Hemoglobin C Disease

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Sickle cell-hemoglobin C disease is an unusual entity that has been reported to occur with a frequency of 1:1,500 in Negroes.1 We recently treated a young girl with this disease who developed major cardiac and pulmonary manifestations of acute rheumatic fever. The lesions of the rheumatic process were demonstrated at postmortem examination. So far as we are aware, there are no other reports in the literature documenting the existence of these two disease states in the same patient.

Case Report

A 14-year-old Negro girl was admitted to the Graduate Hospital of the University of Pennsylvania for the fifth time on December 19, 1962, with a chief complaint of increasing exertional dyspnea of 4 weeks’ duration.

Her four previous admissions were from 1956 to 1958, for extensive burns. She had not required blood transfusion previously. She had been known to have sickle cell-hemoglobin C disease since childhood. There was no prior history of rheumatic fever or scarlet fever.

Approximately 4 weeks prior to admission, the patient noted symptoms of an upper respiratory infection with pharyngitis. Two weeks later she complained of swallowing and pain in her right knee that lasted 3 days. This was followed by pain in the right elbow and wrist without swelling. Increasing exertional dyspnea associated with paroxysmal nocturnal dyspnea and intermittent, nonpleuritic chest pain were also present during the 4 weeks before hospitalization. Moderately severe nosebleeds occurred 37 and 36 days prior to admission.

Physical examination revealed an apprehensive girl who was moderately dyspneic at rest, with a respiratory rate of 30 per minute. The oral temperature was 101 F. The weight was 89 lb. Multiple burn scars with keloid formation were noted on the abdomen, legs, back, and arms. The lung fields were normal to percussion and auscultation. The point of maximal impulse was palpable in the sixth left intercostal space in the anterior axillary line. There were palpable thrills in the mitral and pulmonic areas. The heart rate was 160 per minute, and gallop rhythm was audible over the entire precordium. A grade-III (of VI) harsh, pulmonic systolic murmur, and a grade-V, high-pitched apical systolic murmur were present. There was no venous distention, hepatomegaly, splenomegaly, arthritis, subcutaneous nodules, or erythema marginatum, and the remainder of the physical examination was within normal limits.

Admission laboratory studies revealed a hemoglobin of 9.7 Gm./100 ml, a hematocrit level of 29, and a white-cell count of 6,900/mm.3, with a normal differential count. Moderate target-cell formation was observed in the peripheral smear and 5 nucleated blood cells/100 white blood cells were noted. The reticulocyte count was 1.6 per cent, a sickling preparation was positive, and hemoglobin electrophoresis revealed the presence of S and C hemoglobins. The sedimentation rate was 36mm./hour (Westergren). A urinalysis was normal. The antistreptolysin-O titer was 833 Todd units and the “C” reactive protein was positive. Test for rheumatoid factor, LE preparations, Coombs test, and febrile agglutinins were negative. Blood urea nitrogen, electrolytes, and bilirubin were normal. A throat culture was positive for group-A streptococcus. An electrocardiogram revealed sinus tachycardia, prolongation of the P-R and Q-T intervals, and left ventricular hypertrophy. X-ray demonstrated biventricular and left atrial enlargement.

The patient was placed at bed rest in an oxygen tent. A low-salt diet, digoxin, and mercurial diuretics were given. Intramuscular procaine penicillin, 1.2 million units, was administered daily. On the second hospital day, prednisone, 80 mg. daily in divided dosage, was started because of a presumptive diagnosis of acute rheumatic fever with carditis. This level of prednisone was maintained for 19 days and salicylates were also

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given without significant clinical improvement. The corticosteroid was tapered and eliminated over the course of the next 12 days. Adrenocorticotropic hormone was given in gradually decreasing amounts for a period of 13 days. This hormone was employed because of the apparent failure of all other modalities of therapy, and in an effort to prevent adrenal exhaustion during prednisone withdrawal.

Nonpleuritic left-sided chest pain, tachypnea, basilar rales, left-sided bronchial breathing, hepatic enlargement, fever of 101.4 F., and nosebleeds occurred over a prolonged, worsening course.

On the forty-sixth hospital day, gross hematuria developed, and the hemoglobin and hematocrit level fell to 8.5 Gm. per cent and 27, respectively. One unit of packed red cells was given on the following day. On the forty-eighth hospital day, the patient had a severe bout of abdominal pain and suddenly died.

The heart weighed 430 Gm. There was marked left ventricular hypertrophy, and both ventricles were dilated. The aortic leaflet of the mitral valve was thickened along its free edge. The posterior leaflet showed a few small, wart-like nodules along its atrial surface. The chordae tendineae were thickened and shortened. The tricuspid valve was also thickened. Its septal leaflet showed nodules similar in appearance to those on the mitral valve (fig. 1). The endocardium of the left atrium was thickened and finely granular on its lateral and posterior aspects. Microscopically, scattered Aschoff bodies were easily demonstrable throughout the myocardium (fig. 2).

Fibrous pleural adhesions were noted in the right hemithorax. The right lung weighed 580 Gm. and the left, 520 Gm. They were voluminous and of firm, rubbery consistency throughout. Their color ranged from bright red to shades of bluish-red and rusty brown. The cut surfaces were flat and showed yellowish patches with hemorrhagic zones. Microscopically, there were areas of alveolar hemorrhage, both fresh and old. The pulmonary capillaries, i.e., the alveolar walls, offered a complete range of changes. In places there was hypercellularity of the endothelial layer, and the "septal" or pericapillary cells were increased in number (fig. 3). Fresh fibrin thrombi were also seen, and there seemed to be a gradual transition to fibrosis (fig. 4). A layering of an eosinophilic, fibrin-like substance was observed, forming a "hyaline membrane" within many alveoli. This substance, which

Figure 1
Close-up of tricuspid valve with nodule in middle leaflet and thickened chordae.

Figure 2
Large Aschoff body at center, smaller one near top left corner. (Hematoxylin and eosin stain.)

Figure 3
Proliferative reaction of alveolar capillaries and septal cells. (Hematoxylin and eosin stain.)
stained in a manner identical to the capillary thrombi, appeared to be continuous with these thrombi in places. Masson bodies were present. On the whole the microscopic picture was typical of rheumatic pneumonitis.

One of the most striking findings was that of extreme splenic atrophy (fig. 5). The spleen was reduced to a very small, fibrotic nodule, which could only be identified by following the course of a very atrophic splenic artery. Histologic examination of the spleen revealed fibrosis with marked iron and calcium deposition.

Grossly, the other organs showed only severe congestion. Microscopically, the capillaries of all organs were filled with sickled erythrocytes (fig. 6). This finding was most marked in the liver and kidneys.

Discussion

The problem of distinguishing the clinical manifestations of homozygous-S disease, or sickle cell-hemoglobin C disease, from those of acute rheumatic fever is, at times, an exceedingly difficult one. The presence of joint pain, nosebleeds, abdominal pain, cardiac murmurs, tachycardia, cardiac enlargement, abnormalities of atrioventricular conduction, anemia, and positive “C” reactive protein has been described in these hemoglobinopathies, as well as in acute rheumatic fever.2-7 Hook and Cooper,5 reporting on 52 patients with SC and SS diseases, stated that a diagnosis of acute rheumatic fever or rheumatic heart disease was considered in 50 per cent of their patients. Klinefelter,7 reporting on 11 fatal cases of sickle-cell disease, stated that in three of these patients an antemortem diagnosis of rheumatic heart disease was made, which was not confirmed at autopsy.

Primary cardiac pathology in sickle cell-hemoglobin C disease is said to be uncommon. In two series of cases with sickle cell-hemoglobin C disease totaling 34 patients, 15 patients had systolic murmurs that were gen-
generally not of sufficient intensity to suggest valvular heart disease.\textsuperscript{2,4} Electrocardiograms taken in most of these individuals were normal. River et al.,\textsuperscript{6} reporting upon 75 cases of sickle cell-hemoglobin C disease stated that cardiac murmurs were uncommon in their patients except for soft systolic murmurs. One patient was thought to have murmurs typical of mitral insufficiency and mitral stenosis, but further documentation of rheumatic heart disease was lacking. Sixteen patients who were normotensive in this group had normal electrocardiograms. Six of eight patients who were also hypertensive had nonspecific electrocardiographic abnormalities. It is also of some interest to note that 30 patients in this series had 46 episodes of pneumonitis. The authors thought that the high incidence of lung disease was due to sickling within the pulmonary vasculature. No patient in this group had chronic pulmonary disease. Edington,\textsuperscript{8} reporting on three autopsied cases of sickle cell-hemoglobin C disease, stated that the hearts of his patients were all normal.

The presence of cardiac murmurs in patients with sickle-cell hemoglobinopathy certainly does not indicate organic valvular disease, inasmuch as many of these individuals are moderately anemic. In addition, it has been demonstrated that some patients with this disease have low arterial oxygen saturation (possibly on the basis of intrapulmonary shunting of blood) with a compensatory increase in blood volume and cardiac output. These factors may contribute to the presence of heart murmurs in these patients.\textsuperscript{9}

The coexistence of rheumatic heart disease and sickle-cell anemia has been documented pathologically at postmortem examination in at least seven patients.\textsuperscript{10-12} In addition, Aycock and Weston\textsuperscript{13} reported a 7-year-old Negro boy with sickle-cell anemia who had two major manifestations and several minor manifestations of acute rheumatic fever, and who responded well to salicylates. Uzsoy\textsuperscript{12} recently reported three cases of apparent rheumatic heart disease and sickle-cell anemia, two of whom survived. Although the diagnosis of acute rheumatic fever or rheumatic heart disease has been considered in other patients with sickle cell-hemoglobin C disease, we are unaware of any case in the literature where pathologic confirmation of the coexistence of the two diseases was presented.

The diagnosis of sickle cell-hemoglobin C disease in our patient was based upon two hemoglobin electrophoreses which revealed only S and C hemoglobins as well as several positive sickling preparations. Although 60 to 72 per cent of patients with sickle cell-hemoglobin C disease in reported series have had clinical or postmortem evidence of splenomegaly, the presence of a tiny, atrialithic spleen as was found in our patient has been reported on a number of occasions.\textsuperscript{1,14-18}

The clinical diagnosis of acute rheumatic fever was based upon a history of migratory polyarthritis, the presence of carditis as manifested by x-ray, electrocardiographic, and clinical evidence of cardiac enlargement, organic heart murmurs, persistent tachycardia, gallop rhythm, the presence of palpable thrills, and disturbance in atioventricular conduction. In addition, the patient's history of sore throat, which antedated the joint and cardiac symptoms by about 2 weeks, the presence of group-A streptococcus on throat culture, and the occurrence of epistaxis, fever, elevated antistreptolysin-O titer, positive "C" reactive protein, and increased sedimentation rate in a patient who would normally be expected to have a low sedimentation rate, weigh heavily in favor of a diagnosis of acute rheumatic fever with carditis. The pathologic findings of endocarditis involving the mitral and tricuspid valves, fresh Aschoff bodies in the myocardium, and rheumatic pneumonitis, confirm the clinical impression.

A puzzling feature of this case was the failure of the rheumatic process to respond to large doses of corticosteroids, adrenocorticotrophic hormone, and aspirin as well as the other therapeutic agents that were employed. We believe the failure may in part be explained by postulating the existence of a continuing state of sickle-cell crisis, possibly initiated by the streptococcal infection and promulgated by the presence of rheumatic fever.
and carditis. In support of this view is the autopsy finding of massive numbers of sickled erythrocytes in the pulmonary capillaries and in the blood vessels of other parenchymal organs, especially the liver and kidneys. Also there was an extreme degree of splenic atrophy, presumably secondary to repeated infarctions. These findings could explain the intermittent nonpleuritic chest pain, the severe abdominal pain, and the hematuria that were a prominent feature of the clinical picture. Although there was neither gross nor microscopic evidence of adrenal atrophy post mortem, we cannot completely exclude the possibility that adrenal insufficiency played a role in the patient’s demise.

Summary

The clinical and postmortem findings in a case of sickle cell-hemoglobin C disease complicated by acute rheumatic fever with accompanying carditis, and rheumatic pneumonitis are presented and discussed. This is believed to be the first such case reported.

The recent literature pertaining to the cardiac manifestations of SS and SC hemoglobinopathies is briefly reviewed.

A possible explanation for the failure of the rheumatic process to respond to conventional therapy in our patient is given.

References

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