Retroperitoneal fibrosis in three siblings with the sickle cell trait


Summary: Three West-Indian black siblings with the sickle cell trait developed retroperitoneal fibrosis, a previously unreported association. Other well known renal manifestations associated with the sickle cell trait were also present in some of these cases and included renal medullary necrosis and spontaneous hematuria. It is postulated that the sickling of the erythrocytes in the perireteral vessels resulted in thrombosis, ischemia, reactive scarring and progressive fibrosis indistinguishable from the known histological picture of retroperitoneal fibrosis. The finding of fibrin thrombi in the small veins of the fibrotic tissue of one of these patients would support this explanation.

Patients with the sickle cell trait (the heterozygous AS hemoglobinopathy) occasionally develop renal manifestations which include spontaneous hematuria,\(^1\)\(^2\) hypotension,\(^3\) renal medullary necrosis,\(^4\) pyelonephritis\(^5\) and renal infarction.\(^6\) We have recently observed the occurrence of retroperitoneal fibrosis in three West-Indian black siblings with the sickle cell trait, two of whom also had the radiological features of renal medullary necrosis. The presence of retroperitoneal fibrosis was documented at laparotomy in two of the siblings, whilst the third member of the family has the early radiological features of the disease.

The description of the three cases, the relevant information available on the other members of the family, and a discussion of the possible role of the sickle cell in the pathogenesis of the retroperitoneal fibrosis, are presented in this report.

Case reports

Case 1

Mrs. J.L., a 28-year-old black woman, presented in May 1970 complaining of low-back pain, frequency, periodic nocturia, urgency and fatigue of one month's duration. Her past illnesses included infectious hepatitis, cystitis, and an anaphylactic reaction to penicillin, all in 1962. She had one normal term pregnancy in 1966. Her medications have included an analgesic-sedative combination (butalbital-cafeine-aspirin-phenacetin) for tension headaches, antihistamines for urticaria and sulfisoxazole for the urinary tract infection. She denied exposure to ergot alkaloids or methysergide.

Results of the physical examination were negative except for slight puffiness of the lower eyelids and a grade 2/6 systolic ejection murmur at the lower left sternal border.

The laboratory results included a normal hematocrit, erythrocyte sedimentation rate (ESR) of 25 mm./hr. and leukocyte count of 7000/c. mm. with a normal differential. The blood smear indicated the presence of anisocytosis, poikilocytosis and target cells. The sickle cell preparation demonstrated sickling. The urinalysis was negative for albumin and sugar, the specific gravity was 1.012, the microscopic examination revealed the presence of granular casts and scattered leukocytes, and the culture was sterile. The endogenous creatinine clearance and 24-hour urinary protein estimations were within normal limits. The concentrations of blood urea nitrogen, serum creatinine and electrolytes were all normal.

An intravenous pyelogram (IVP) and retrograde pyelogram showed bilateral hydrenephrosis and hydroureter above the third lumbar vertebra (Fig. 1A) with narrowing and medial displacement of both ureters below this level. An inferior vena cavogram appeared normal. Bilateral ureterolysis was performed and the ureters were intraperitonealized. At operation it was noted that in addition to the slight degree of retroperitoneal fibrosis present, the major lesion was a marked periureteral hose-like fibrous sheath involving both ureters, a variant of retroperitoneal fibrosis termed periureteritis plastica.\(^7\)\(^8\) The pathological and immunological findings will be discussed later.

The patient had no amelioration of her symptoms after the operation, and an IVP performed four months later revealed an increase in the degree of hydrenephrosis. She was given methylprednisolone 32 mg. daily for four months with some transient symptomatic improvement, but a repeat IVP (Fig. 1B) showed no reduction in the increased degree of hydrenephrosis noted postoperatively. The methylprednisolone was discontinued and the patient is being kept under observation without therapy and manages to live a normal life despite the low-back discomfort.

From the Departments of Medicine, Radiology and Pathology, Queen Elizabeth Hospital, McGill University, Montreal

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Reprint requests to: Dr. James A. Phills, Queen Elizabeth Hospital, 2100 Marlowe Ave., Montreal 260, P.Q.

Case 2

Mr. H.A., a 25-year-old brother of the patient in case 1, was admitted to hospital in October 1968 after two episodes of gross hematuria in the previous two weeks. Past medical history was negative and in particular there was no history of drug ingestion except for a one-week course of penicillin for tonsillitis in February 1968. Physical examination yielded entirely normal findings. Results of hematological and biochemical laboratory investigations including renal function studies were normal.

Microscopic examination of the urine showed many erythrocytes but no casts. The sickle cell preparation demonstrated sickling. The IVP and retrograde pyelogram showed bilateral hydronephrosis and hydro-ureter above the third lumbar vertebra with narrowing and medial displacement of both ureters below this level. The renal arteriogram and lymphangiogram appeared normal. Bilateral ureterolysis was performed and the ureters were intraperitonealized; marked retroperitoneal fibrosis of the classical type was noted at operation. An IVP performed three years after operation showed persistence of the hydronephrosis, and also indicated the presence of renal medullary necrosis (Fig. 2). The patient continues to have some mild low-back pain and fatigue but is able to lead a normal life. He has had no recurrence of his hematuria.

Case 3

Miss Y.A., a 21-year-old sister of the above patients, presented with low-back discomfort and fatigue. She had taken on occasion some unknown sedatives for functional complaints, but only for short periods of time. Results of biochemical and hematological laboratory investigations were normal except for a positive sickle cell preparation. The urinalysis also yielded normal findings. An IVP indicated early dilatation of the right pyelocalyceal system and both ureters above the fifth lumbar vertebra with narrowing below this level (Fig. 3A) as well as slight medial displacement. There was also evidence of medullary necrosis of both kidneys (Fig. 3B). A follow-up IVP a year later showed no change. The patient is being observed without therapy.

Special studies

A. Family survey

The three siblings were members of a black family from Guyana which included a mother and father and eight children. The family pedigree did not indicate any consanguinity of the parents. We were unable to contact three of the siblings and only limited studies were possible on the father and the two other siblings who are still living in Guyana. The pertinent hematological and urological data available on the parents and the five siblings studied are set forth in Table 1. The father, aged 67, who has the sickle cell trait, had a bout of hematuria in 1945; his IVP did not suggest the presence of retroperitoneal fibrosis but there was evidence of bilateral chronic pyelonephritis. The mother had normal findings on hemoglobin electrophoresis and a normal IVP. The eldest sibling, Mr. K.A., aged 38, also has the sickle cell trait. He has no complaints except occasional low-back

FIG. 1B—IVP from case 1 after

four months of methylprednisolone therapy and eight months after operation. Note that the intraperitonealized ureters are in a markedly lateral position. The hydronephrosis has apparently increased; however the drainage appears satisfactory along the distal uninvolved ureters.

FIG. 2—IVP from case 2 three years after bilateral ureterolysis. Note that the bilateral hydro-ureter and hydronephrosis are still present. Small medullary cavities are present adjacent to the two lower right calyces (arrows).

FIG. 3A—IVP from case 3. Early bilateral hydronephrosis and hydro-ureter with slight medial displacement of both ureters. Small medullary cavities in two lower calyces of right kidney (arrows).

FIG. 3B—Detailed view of IVP from case 3. Medullary cavities in lower calyces of both kidneys (arrows) are consistent with widespread medullary necrosis.
pain. He refused to submit to an IVP. Mr. D.A., aged 32, has the sickle cell trait. He is in good health and his IVP appeared normal. Quantitative determinations of the amount of hemoglobin S in the three siblings with retroperitoneal fibrosis yielded levels of 38 to 40%. The serum hemoglobin and haptoglobin levels were normal in these cases.

B. Results of immunological and pathological studies

The patient in case 1 had moderate polyclonal hypergammaglobulinemia (Table II). Her serum β-C component level was normal and the lupus erythematous preparations yielded negative results. However, antinuclear antibody was present in her serum at a dilution of 1:20 in a speckled pattern as demonstrated by the immunofluorescence technique. Results of other studies including rheumatoid factor, cold agglutinins, cryoglobulins, cryofibrinogens, and Wassermann and Coombs' tests were negative.

Microscopic examination of the fibrous tissue specimen removed at operation in case 1 disclosed the presence of connective tissue (Fig. 4A) with abundant collagen and an inflammatory infiltrate. Although the infiltrate was predominantly of the chronic type, polymorphonuclear leukocytes were also seen in some areas clustered in and around the vessels, suggesting a non-necrotizing vasculitis (Fig. 4B).

Immunofluorescence studies of the tissue identified deposits of immunoglobulins IgG and IgM and fibrin in a granular pattern along the basement membrane of small vessels. The β-C component of complement was not detected.

An interesting finding was the presence in some biopsy sections of fibrinoid aggregates arranged in laminar fashion in or around the walls of veins, as is seen in many thrombi. They were demonstrated by special fibrin stains (Fig. 4C).

Aside from the moderate polyclonal hypergammaglobulinemia, all the other immunological studies listed above were negative in case 2. Histological study of the biopsy specimen from case 2 showed markedly increased fibrosis with perivascular mononuclear cell infiltration. Immunofluorescence studies showed no deposits of immunoglobulins, complement or fibrin in the biopsy specimen. The only positive immunological finding in case 3 was minimal hypergammaglobulinemia (Table II).

Discussion

In this study we have presented a black family in which the father and all the siblings we have been able to contact have the sickle cell trait. Of the three siblings studied in more detail, two have radiological evidence of renal medullary necrosis, a lesion characteristically associated with sickle cell trait. One of these patients (case 2) presented with hematuria which was likely caused by renal medullary ischemic necrosis. However, in addition, these three siblings also presented symptoms and radiological findings indicating the presence of retroperitoneal fibrosis—a non-specific clinical picture of low-back pain and fatigue, along with the classical radiological triad of hydronephrosis, mid-ureteral obstruction and medial deviation of the ureters. There are many reports of the renal manifestations of the sickle cell trait;4,9,10 but our cases are unique in that an association between sickle cell trait and retroperitoneal fibrosis has not been previously described.

Table II

<table>
<thead>
<tr>
<th>Immunological studies</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (800-1600 mg./100 ml.)*</td>
<td>2500</td>
<td>2900</td>
<td>1780</td>
</tr>
<tr>
<td>IgA (75-420 mg./100 ml.)*</td>
<td>450</td>
<td>500</td>
<td>460</td>
</tr>
<tr>
<td>IgM (50-200 mg./100 ml.)*</td>
<td>305</td>
<td>550</td>
<td>250</td>
</tr>
<tr>
<td>β-C (125-175 mg./100 ml.)*</td>
<td>175</td>
<td>155</td>
<td>135</td>
</tr>
<tr>
<td>Antinuclear antibody by immunofluorescence</td>
<td>Positive 1/20</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Immunofluorescence studies of tissue biopsy</td>
<td>Granular deposits of IgG and IgM</td>
<td>Negative</td>
<td>—</td>
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*Normal concentrations

Table I

<table>
<thead>
<tr>
<th>Pertinent hematological and urological data</th>
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<tbody>
<tr>
<td>Patients, age</td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>Mother (63)</td>
</tr>
<tr>
<td>Siblings:</td>
</tr>
<tr>
<td>K.A. (38)</td>
</tr>
<tr>
<td>J.L. (28)</td>
</tr>
<tr>
<td>(case 1)</td>
</tr>
<tr>
<td>H.A. (25)</td>
</tr>
<tr>
<td>(case 2)</td>
</tr>
<tr>
<td>Y.A. (21)</td>
</tr>
<tr>
<td>(case 3)</td>
</tr>
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</table>

*Only qualitative determinations available
The cause of retroperitoneal fibrosis is unknown. Some possible etiologic mechanisms are reviewed by Ormond. The most common association is prolonged methysergide ingestion, but the pathological mechanism is not known. There are many cases reported which suggest an autoimmune vasculitis as the cause. It is probable that the disorder has no single origin. In support of this concept is our proposal that the retroperitoneal fibrosis in these siblings was a consequence of the sickle cell trait. Other possible etiologic mechanisms in these cases that merit some discussion include genetic factors, drug exposure and immunological mechanisms.

The role of genetic factors was not studied in this family, and only in multifocal fibrosclerosis, a term used to describe a group of fibrosing conditions including chronic mediastinal fibrosis and retroperitoneal fibrosis, has evidence been presented that the disease is genetically determined. The presence of consanguinity in the parents of the patients affected with multifocal fibrosclerosis reported by Comings et al strongly suggested the autosomal recessive form of inheritance in that family. Consanguinity was not present in the parents of the siblings reported in this paper.

There was no history of ingestion of methysergide, ergot alkaloids or other vasoconstrictor drugs in these cases. However, since the discontinuation of methysergide therapy has been associated with regression of the pathologic process, all drug therapy in the three siblings was discontinued for one year; repeat IVPs showed no change in the degree of hydronephrosis at the end of this time. This finding plus the absence of history of prior intake of such drugs suggest strongly that adverse reaction to drugs did not play a role in the fibrotic process. Graham et al have reviewed the possible mechanisms by which methysergide may influence the development of retroperitoneal fibrosis; its powerful vasoconstrictor action may have a prominent influence.

It is possible that vasoconstrictor drugs, by restricting the circulation to various organs, may promote the development of ischemia and hypoxia—a milieu that enhances the sickling process. Therefore, these drugs have the potential of enhancing not only retroperitoneal fibrosis but all lesions associated with sickle cell trait or disease. The patients have been cautioned against taking vasoconstrictor drugs.

The three siblings all had mild polyclonal hypergamaglobulinemia. The cause is unclear, but may be an immune response to a low-grade renal infection secondary to ureteral stasis. Such an infection was not confirmed by bacteriologic studies, but the presence of granular casts and many leukocytes in the urine of patient 1 suggests an infective process. Renal infection is not infrequently found in patients with sickle cell trait and in this context it is of interest that the father had chronic pyelonephritis.

Only patient 1 had evidence of an autoimmune mechanism—antinuclear antibody in her serum and

![FIG. 4A](image1)
**FIG. 4A—Case 1. Retroperitoneal tissue biopsy showing extensive fibrosis. Hematoxylin and eosin: original magnification x 100.**

![FIG. 4B](image2)
**FIG. 4B—Case 1. Retroperitoneal tissue biopsy. Inflammatory infiltrate more marked in and around vessels. Hematoxylin and eosin: original magnification x 100.**

![FIG. 4C](image3)
**FIG. 4C—Case 1. Retroperitoneal tissue biopsy. Fibrin stains demonstrate presence of fibrin thrombi in and around walls of veins. Phosphotungstic-acid hematoxylin: original magnification x 400.**
minimal vasculitis in the fibrotic tissue, detectable by light and immunofluorescent microscopy. However, no such evidence was found in the other two siblings, and since it is probable that a common pathogenetic mechanism is operative in all three siblings, an immune mechanism is not likely the primary cause of retroperitoneal fibrosis in these cases. A not unreasonable proposal is that the reduced blood supply to the retroperitoneal tissue in case 1, a consequence of the obstructed vessels, may have given rise to altered nuclear antigens which elicited the immune response observed. The vasculitis may, however, have contributed to the severity of the fibrosis in this patient since she had by far the most marked degree of hydrenephrosis.

Retroperitoneal fibrosis has been treated with corticosteroids with variable results, 39-42 and occasionally with success, particularly if there was an active inflammatory component. The lack of response of patient 1 to corticosteroid therapy further supports the suggestion of a secondary role for the vasculitic process. In fact, the results of our therapeutic attempts in these cases suggest that neither operation nor corticosteroid therapy offers any benefit to patients that have retroperitoneal fibrosis associated with the sickle cell trait.

We propose that the finding of retroperitoneal fibrosis, an uncommon disorder, in the three siblings with the sickle cell trait is not a coincidence. Renal medullary necrosis, a lesion characteristically associated with the sickle cell trait, was also present in two of these patients and it is not unreasonable to postulate that both lesions were initiated by the intravascular sickling process. Hyperosmolarity in the renal medulla is considered to be the operative factor in sickling in the kidney, 43-44 and it is likely that the unknown factors causing the periureteral intravascular sickling are different from those within the kidney. The occurrence of extrarenal lesions is not unique to these cases; extrarenal infarcts have been reported in patients with the sickle cell trait. 4 Therefore, there is no a priori reason why this could not happen in the periureteral vessels as well. We postulate that the sickling in the periureteral vessels resulted in thrombosis with ischemia, followed by reactive scarring and progressive fibrosis indistinguishable from the known histological picture of retroperitoneal fibrosis. The presence of fibrin thrombi in and around the vessels of the fibrotic tissue of patient 1 would support this explanation.

The authors are grateful to Dr. Enid Denbow for the clinical information she provided on the members of the family living in Guyana, W.I.

Résumé

Fibrose rétropéritonéale observée chez trois frères germains atteints de drépanocytose

On a découvert une fibrose rétropéritonéale chez trois membres d’une même fratrie, noirs Antillais, qui souffraient de drépanocytose. Cette association ne semble pas avoir été déjà rapportée. D’autres manifestations rénales bien connues et caractéristiques de l’anémie falciforme se retrouvaient chez certains et comportaient notamment une nécrose médullaire des reins et de l’hématurie spontanée. Il est permis de supposer que la formation des érythrocytes falciformes dans les vaisseaux rénaux s’est traduite par de la thrombose, de l’ischémie, des cicatrisations réactives et une fibrose progressive qui ne pouvaient être distingués du tableau histologique bien connu de la fibrose rétropéritonéale. La découverte de caillots de fibrine dans les veines du tissu fibrosé chez un des malades tendrait à confirmer cette explication.

References

7. VEST SA, BARLEONE B: Periureteritis plastica: report of 4 cases. J Urol 70: 38, 1953