Pediatric Sarcoidosis Presenting with Hypertensive Encephalopathy

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Abstract

A 3-year-old girl with simultaneous presentation of hypertensive encephalopathy, subcutaneous nodules, hepatosplenomegaly and proteinuria was presented. The sarcoidosis was confirmed by histologic demonstration of non-caseating granulomas in the liver, left kidney, a cervical lymph node and subcutaneous nodules. The proteinuria resolved spontaneously. During the six-month period of steroid therapy, the renal mass and hepatosplenomegaly were dissolved but the cervical lymphadenopathy still persisted. The hypertensive state was difficult to control which required a multiple antihypertensive drug regimen.

Sarcoidosis is a chronic, multisystem disease of unknown etiology infrequently reported in children[1,2]. Sarcoidosis in children was not comprehensively described until 1956 when Mc Govern and Meritt[3] reviewed 104 cases under 15 years of age in the literature. The majority of cases of renal impairment in sarcoidosis are attributed to associated hypercalcemia, hypercalciuria and nephrocalcinosis[4-6]. Primary glomerular disease has not been generally considered a part of the spectrum of systemic sarcoidosis. Membranous glomerulonephritis has been reported most frequently, followed by proliferative and progressive glomerulonephritis[7-12]. However, there are reports of generalized sarcoidosis and renal impairment due to sarcoid infiltration without nephrocalcinosis[13,14]. Here, we report the case of a patient presenting with generalized sarcoidosis accompanied by hypertensive encephalopathy.

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CASE REPORT

A 3-year-old girl was admitted to Chulalongkorn Hospital on August 23, 1996 with an episode of generalized tonic-clonic convulsion lasting about twenty minutes. During the night before admission, she suddenly woke up due to headache, blurred vision, projectile vomiting and generalized seizure. She had been well upto about three months previously, since that time she had developed multiple subcutaneous nodules at the scalp, anterior chest wall and abdomen. Hepatosplenomegaly, enlarged axillary and post auricular lymph nodes were noticeable at this time. The tuberculin test (5 TU purified protein derivative) was negative and chest X-ray was normal Biopsies of the cervical lymph node and scalp nodule revealed non-caseating granuloma (Fig. 1, 2). Bone marrow aspiration showed megaloblastic changes of the erythroid series.

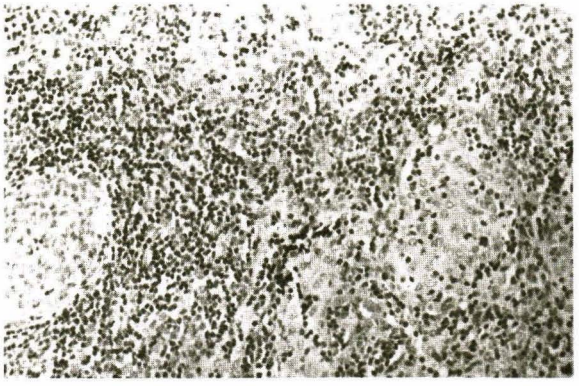


Fig. 1. Biopsy specimen of a cervical lymph node demonstrating non-caseating granulomas. (H & E x 200)

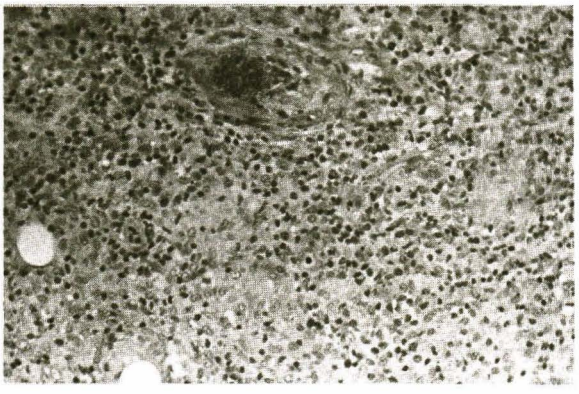


Fig. 2. Biopsy specimen of a scalp nodule showing non-caseating granulomas. (H & E x 200)

She was the first-born of two children. Her previous medical history was not remarkable and there was no history of tuberculosis in her family.

On admission, she was drowsy, body weight was 12.4 kg (30th percentile), height 93 cm (50th percentiles), head circumference 48 cm (50th percentile). Vital signs were body temperature 37.5°C, pulse rate 170/min, respiratory rate 28/min and blood pressure 190/130 mmHg. Eyes, ears, nose and throat were normal. An examination of the chest and cardiovascular system revealed no abnormalities. The abdomen was soft, the liver was palpable 2 cm below the right costal margin. The bimanual palpation was positive at the left flank without tenderness. A few clustered, non-tender-lymph nodes 0.5 cm in diameter were palpable in the left anterior cervical triangles and both inguinal regions. A neurological examination was unremarkable.

Investigations

A complete blood count revealed a hematocrit of 46%, a WBC of 28,800/mm^3 with PMN 78%, lymphocytes 12%, monocytes 7% and basophils 3%, and a platelet count of 337,000/mm^3. A sedimentation rate of 59 mm per hour. A dipstick urinalysis showed a 4+ of protein. The urine specific gravity was 1.026, pH 6, no RBC and WBC were detected on microscopic examination. Blood urea nitrogen was 12 mg/dL, serum creatinine 0.5 mg/dL, Na 130 mEq/L, K 3.3 mEq/L, Cl 94 mEq/L, CO_2 25 mEq/L, Ca 9.1 mg/dL, PO_4 2.9 mg/dL. Total serum protein was 7.9 g/dL and albumin 4.7 g/dL. The liver function test was normal. CH_{50} was 48 units/mL (normal 19-40) and ß1C 179 mg/dL (normal 101-186). Antinuclear antibodies, C-reactive protein, anti HIV, VDRL, anti Epstein-Barr virus (IgG and IgM) were all negative results. The radial immunodiffusion revealed IgG of 1420 mg/dL (normal 500-1350), IgA 122 mg/dL (normal 35-220) and IgM 86.9 mg/dL (normal 38.4-144). T-cell count revealed 936 cells/mm^3 (normal 2400 ± 500), T_4 (helper) 449 cells/mm^3 (normal 730 ± 190), T_8 (suppressor) 84 cells/mm^3 (normal 696 ± 168), T_4/T_8 ratio was 5.3 (normal 1.35 ± 0.48), serum angiotensin converting enzyme acti-

vity measured by using hippuryl-L-histidine-L-leucine as substrate[15] was 10.32 units/mL serum (normal 15-40). The 24-hour urine volume was 1700 mL, urinary protein 1.65 g/day (125 mg/m^2/h), creatinine clearance 120.5 mL/min/1.73 m^2, FECa 2.0% (normal < 0.5%). The urine vanillylmandelic acid 3.6 mg/total volume (normal 0.7-6.8). The polymerase chain reaction for tuberculosis in the urine specimen was negative. An electrocardiogram was consistent with left ventricular hypertrophy. A chest X-ray was unremarkable. The rapid sequence intravenous pyelogram showed prompt excretions bilaterally. There was stretching of the calyx of a left upper pole without distortion or caliectasis. The right pelvicalyceal system appeared normal. Both kidneys were large. The ultrasound examination of the upper abdomen showed hepatosplenomegaly devoid of any intrinsic mass. An isoechoic mass was detected in the left kidney, with its greatest diameter of 1.9 cm (Fig. 3) The color Doppler imaging of the left kidney revealed a poor segmental perfusion of the upper pole. Both renal arteries were normal.

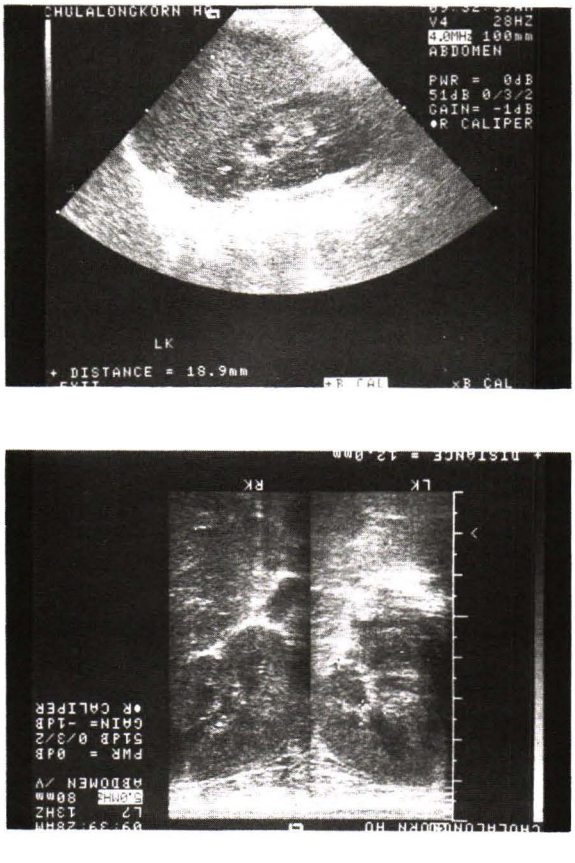


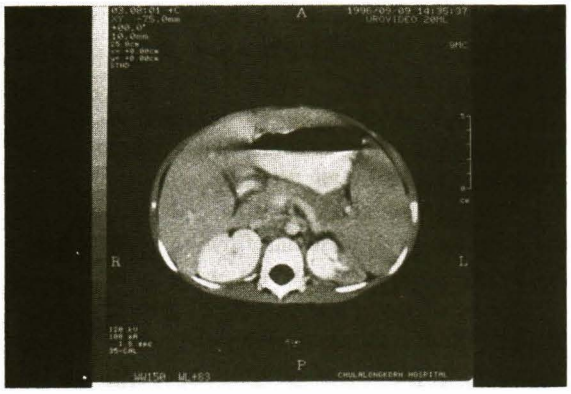
Fig. 3. Longitudinal (A) and transverse (B) supine scans of the kidneys. There was an isoechoic mass in the left kidney with 1.9 cm in diameter.

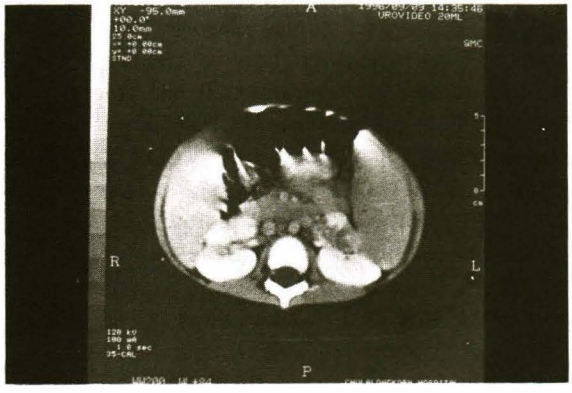
A renogram with pre- and post-captopril test revealed good vascular flow to both kidneys. The accumulation and excretion of both kidneys were satisfactory. There was no evidence of renin-angiotensin dependent renovascular hypertension.

Computer tomography of the brain and abdomen was performed. The intracranial imaging was unremarkable. There was hepatosplenomegaly without space-occupying lesions. Both kidneys had atrophic lobulated contours, especially on the left kidney. There were multiple low-density areas at both the upper and lower poles of the left kidney. An area of low density at the upper pole of the right kidney was also noted. Multiple celiac, mesenteric lymphadenopathy and a retrocaval node were also identified. (Fig. 4)

On October 10, an explorative laparotomy was performed in order to retrieve biopsies of the left kidney, the liver and mesenteric lymph nodes. Sections of the liver tissues (Fig. 5) showed a widening of the portal tracts with mononuclear cells infiltrations. Scattered small granulomas consisting of lymphocytes, mononuclear cells and histiocytes were seen throughout the liver. The test applying CD68 (KP-1) was positive for histiocytes. Sections of the left kidney tissues (Fig. 6) showed mild mesangial hypercellularity along with a few foci of neutrophils. The capillary wall was normal. Scattered interstitial non-caseating granulomas were noted. The fluorescent antibody study showed segmental deposits of IgG (1+), IgA (1+), IgM (1+) in 3 out of 20 glomeruli and scattered deposits of C_3 (1+) in few glomeruli. There was deposition of C_{1q} (1+) in the mesangial area of all glomeruli. Neither acid fast bacilli nor fungi were seen in the renal granulomas. The microscopic sections of mesenteric lymph nodes revealed lymphoid hyperplasia devoid of granuloma.

The hypertension was controlled with enalapril, prazosin and minoxidil. Proteinuria resolved spontaneously prior to starting the steroid therapy. During the six-month period of the steroid therapy, the renal mass and hepatosplenomegaly dissolved but the cervical lymphadenopathy still persisted. The most recent 24-hour urine examina-





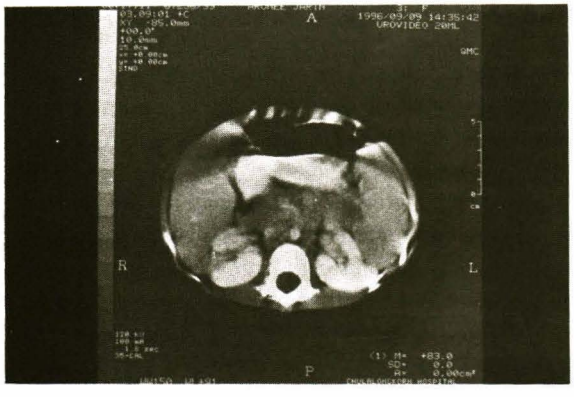


Fig. 4. Computer tomography of abdomen. There were multiple low-density areas at both the upper pole (4A) and lower pole (4B) of the left kidney. An area of low density at the upper pole of the right kidney (4C) was also noted.

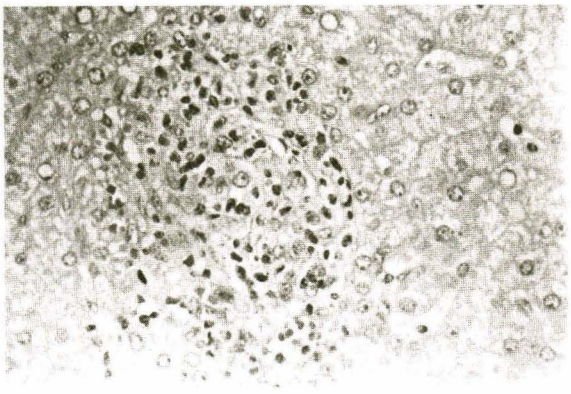


Fig. 5. Section of the liver tissue revealed non-caseating granulomas and slight widening of portal tracts with mononuclear cells infiltrations. (H & E x 400)

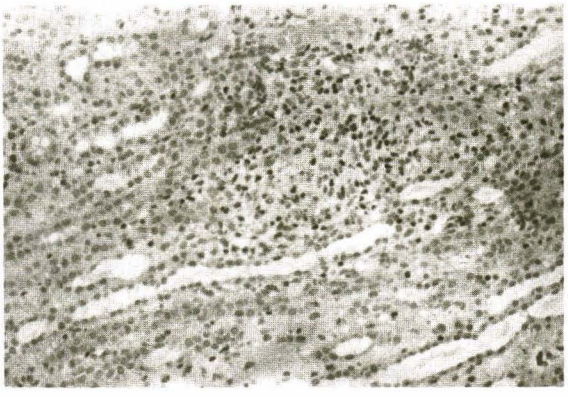


Fig. 6. Biopsy specimen of the left kidney showing scattered interstitial non-caseating granulomas and mild mesangial hypercellularity. (H & E x 200)

tion revealed a urinary protein of 0.07 g/day (5.2 mg/m^2/h) and a creatinine clearance of 158 mL/min/1.73 m^2. The hypertensive state was difficult to control which required a multiple antihypertensive drug regimen.

DISCUSSION

A diagnosis of sarcoidosis is dependent upon the pathologic demonstration of non-caseating granulomas, usually by lymph node or liver biopsy,

and absence of tuberculosis, fungal infections or evidence of malignancy. The Kveim-Siltzbach test[16] is useful as a diagnostic aid, but it is not always successful and not generally available. Our patient demonstrated non-caseating granulomas in a cervical lymph node, a scalp nodule, the left kidney and the liver but we were, unfortunately, not able to perform the Kveim-Siltzbach test on our patient since it was not yet available in Thailand. Tuberculosis could be excluded in our patient by negative tuberculin skin test and negative screening for acid-fast bacilli in gastric washings and tissue specimens. The polymerase chain reaction for tuberculosis in urine also had a negative result.

The sarcoidosis can affect kidneys in several ways[7]. The clinical features of the renal disease may be those of the uremic syndrome. In some instances, accelerated or malignant hypertension may be superimposed[17-19]. We could not find any previous reports of renal sarcoidosis manifesting with hypertensive encephalopathy in children. At the time of admission to the hospital, the evidence of renal damage was prominent. The renal function test revealed a massive proteinuria (> 40 mg/m^2/h). As published elsewhere[20], a mild degree of albuminuria is not unusual in sarcoidosis, but in most cases this is not associated with any additional renal damage. Berger et al[13] reported a great reduction in the excretion of albumin related to cortisone therapy in a patient with renal sarcoidosis but the massive proteinuria in our patient resolved spontaneously prior to starting the steroid therapy. Our patient had hypercalciuria inspite of normal serum calcium level that might indicate increased intestinal calcium absorption due to increased sensitivity to vitamin D[21,22].

The major immunologic changes in sarcoidosis consist of depression of the delayed - type hypersensitivity, hyperreactive antibody responses and the Kveim-Siltzbach skin test phenomenon. There are elevated immunoglobulin levels, increased antibody levels to Epstein-Barr, herpes simplex, rubella, measles and parainfluenza viruses, a heightened immune response to mismatched blood and occasional false-positive Wassermann reactions, but there is no increase in circulating autoantibodies[23]. Our data demonstrated a negative tuberculin test, hyperproteinemia, increased IgG levels, a reduced number of T-lymphocytes, and absence of autoantibodies. Buckley et al[24] drew attention to the elevation of complement activity in patients with active sarcoidosis. They suggested the total complement (CH_{50}) concentration to be increased due to infection. Our patient showed a high level of CH_{50} but revealed no evidence of infection.

An assay of serum angiotensin-converting enzyme (ACE) activity was found useful as an aid in confirming a diagnosis of active sarcoidosis[15]. Enzyme activity is consistently increased in patients with active pulmonary sarcoidosis, in contrast to normal or low levels in patients with other types of chronic lung disease or other types of granulomatous disease. Our patient had low levels of ACE activity which may be due to the absence of pulmonary involvement.

Diagnostic studies for hypertension were performed in our patient. The normal 24-hour excretion rate of vasoactive hormone served as a diagnostic exclusion of pheochromocytoma. Renal imaging examinations used to identify renovascular disease as a cause of a patient's hypertension were all inconclusive.

The mass at the upper pole of the left kidney detected by ultrasonogram and computer tomogram corresponded with the non-caseating granulomas found in the renal tissues. In the present case, the renal involvement of the granulomas of the sarcoid might have been sufficiently widespread to initiate the hypertensive state. Although the etiologic agent(s) responsible for generalized sarcoidosis have not been identified, it is believed that this granulomatous reaction represents a type of immunologic hypersensitivity[23-25]. The glomerular lesions observed in our patient showed mild mesangial proliferation. The fluorescent antibody study revealed a diffuse segmental localization of antihuman immunoglobulins and C3 which was similar to that usually observed in a partially resolved post-infectious glomerulonephritis.

Chronic intrahepatic cholestasis is one of the expressions of hepatic involvement in sarcoidosis[26]. It may be accompanied by portal hypertension. The most prevalent hepatic involvement in sarcoidosis is asymptomatic granulomatous infiltration of which the only expression may be increased serum levels of alkaline phosphatase and impaired bromsulfalein excretion[27]. With our patient the liver biopsy demonstrated non-caseating granulomas, but we found only hepatomegaly without any biochemical changes of the liver function test. Long term follow-up should be recom-

mended due to the risk of cirrhosis ensuing in some cases after a period of time.

The natural history of childhood sarcoidosis with severe granulomatous renal involvement is difficult to elucidate due to the rarity of the disease, its chronicity, and spectrum of organ involvement[1]. The response to corticosteroids is variable but it still remains the most effective treatment in symptomatic patients[28,29]. Little is known about the appropriate duration of therapy in such cases. During the six-month period of the corticosteroid therapy we administered to our patient, the renal mass and hepatosplenomegaly dissolved. The hypertensive state was difficult to control and the patient still needs a multiple antihypertensive drug regimen. It is obvious that the patient will have to be kept under observation for a longer period.

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รายงานผู้ป่วยเด็กสาร์คอยโดสิสชักจากความดันโลหิตสูง

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ผู้ป่วยเด็กหญิงไทยอายุ 3 ปี มีการชักจากความดันโลหิตสูง, ต่อมน้ำเหลืองที่คอโต, มีก้อนเนื้อที่ใต้หนังศีรษะ, ตับม้ามโต และตรวจพบไข่ขาวในปัสสาวะ การวินิจฉัยโรคสาร์คอยโดสิสอาศัยการตรวจพบพยาธิสภาพที่ต่อมน้ำเหลือง, ก้อนเนื้อใต้หนังศีรษะ, ตับ และไต ภาวะไข่ขาวรั่วในปัสสาวะหายได้เอง จากการรักษาด้วย เพร็ดนิโสโลน เป็นเวลา 6 เดือน ก้อนที่ไดหายไป ตับม้าม ขนาดปกติ แต่ต่อมน้ำเหลืองที่คอยังคงโตอยู่ ผู้ป่วยยังคงต้องใช้ยาลดความดันเลือดหลายขนานในการควบคุมภาวะความดันโลหิตสูง

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