Yonsei Medical Journal
Vol. 38, No. 4, pp. 233~235, 1997

☐ Case Report ☐

Cold Haemagglutinin Disease in Systemic Lupus Erythematosus

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A 34-year-old lady presenting with features of cold agglutinin disease during the course of systemic lupus erythematosus is described. Cold antibody titer was very high (1 in 4096) with specificity for 'I' antigen . Even though she had poor prognostic factors like high titer of cold antibodies with low thermal amplitude, she responded well to prednisolone.

Key Words: Cold haemagglutinin disease, systemic lupus erythematosus

Autoimmune hemolytic anaemias are characterized by the presence of antibodies recognizing antigens on the individual's own erythrocytes resulting in immune-mediated hemolysis. Hemolytic anaemia is most often due to autoimmune hemolysis. Hemolytic anaemia is found to occur in 10% of cases of systemic lupus erythematosus (SLE) and rarely it may be the presenting manifestation of the disease. It is usually of the warm antibody type. Occurrence of cold haemagglutinin disease (CHAD) is very rare. We report a case of SLE presenting with cold haemagglutinin disease.

CASE REPORT

A 34-year-old female presented with history of progressive pallor, irregular fever of one month and polyarthritis of 2 years duration. There was no history of swellings in the neck, Raynaud's phenomena, sore throat, skin rash, acrocyanosis or livedo reticularis. On physical examination, she was afebrile, pulse rate was 70/min and BP was 130/80 mmHg. She had pallor, alopecia, mild icterus and oral ulcers. Spleen was palpable 3 cms below the costal margin. Ocular fundi and other systems were within normal limits.

The blood Hgb was 6 gm%, WBC count 14×10^9/l with a differential count of polymorphs 74, lymphocytes 22 and eosinophils 4. ESR was 136 mm/1st hr, platelets 88×10^9/ 1 and reticulocyte count 10%. Urine analysis was normal except for the increased urobilinogen.

Serum bilirubin was 2.7 mg% with direct bilirubin 0.7 mg%. Peripheral smear showed anisocytosis, polychromasia and features of autoagglutination (Fig. 1). Pure saline preparation showed autoagglutiation which disappeared on incubation at 37°C. Blood grouping at room temperature showed autoagglutination. On repeating the test at 37°C agglutination disappeared. The direct Coombs' test was positive with polyspecific antisera. Cold agglutinin titer was 1 in 4,096 at 4°C with specificity for 'I' antigen. Lupus erythematosus (LE) cell test and anti-double stranded DNA antibody test were positive. Paul

Received February 24, 1997
Accepted August 21, 1997
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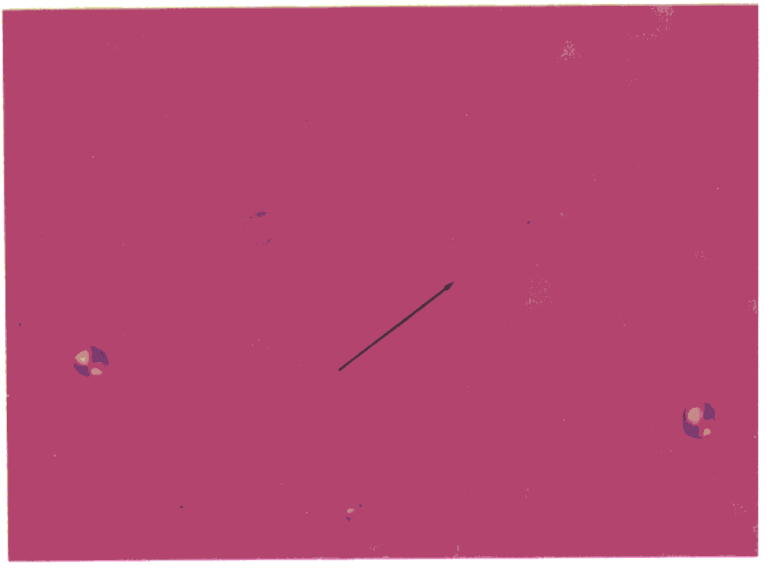

Fig. 1. Polarized light microscopy of synovial fluid demonstrating 7~15 mm-sized positively birefringent maltese cross appearing lipid spherules (magnification ×200, black arrow indicates plane of orienting line of the compensated polarizing microscope).

tender with some limitation of motion. All other joints had full range of motion without warmth, erythema or tenderness. The white blood cell count was 5330/mm^3 with 62.9% neutrophils, 27.3% lymphocytes, 5.7% monocytes and 3.7% eosinophils. The hemoglobin was 14.5 gm/dL, the ESR 95 mm/hour, CRP 4.27 mg/dL and the platelet count 240,000/mm^3. The serum uric acid level was 4.3 mg/dL, the serum fasting cholesterol and triglycerides were 249 mg/dL and 132 mg/dL, with the HDL cholesterol of 49 mg/dL and LDL cholesterol of 174 mg/dL. The fasting blood glucose was 173 mg/dL, 2 hour-postprandial blood glucose was 226 mg/dL, AST was 30 IU/L and ALT was 18 IU/L. Tests for the rheumatoid factor and anti-nuclear antibody were negative. The prothrombin time, activated partial thromboplastin time, electrolytes, amylase and lipase were all normal. X-rays of the left foot showed normal findings without evidence of fracture or chondrocalcinosis. The third metatarso- phalangeal joint was aspirated, and 0.2 cc of blood-tinged fluid was removed. Under polarized microscopy, 1~4 positively birefringent spherules with a maltese cross appearance were seen per high power field (Fig. 1). No other crystals were seen. The patient was given piroxicam, 10 mg bid. Seven days after taking the medicine, his symptoms were much improved. One month later, the patient visited our OPD clinic complaining of severe pain in another site of the left foot. The tender point was the transverse tarsal joint around the cuboid bone. Arthrocentesis was performed and 0.1cc of fluid was aspirated. Also, under polarized microscopy, positively birefringent spherules with a maltese cross appearance were seen again. No other crystals were seen. Therapy was continued with piroxicam, 10 mg bid. On the patient's next visit 14 days later, his pain had subsided and the tenderness was gone. He continued to do well 3 months later without NSAID.

DISCUSSION

This is a case of monoarthritis associated with large numbers of positively birefringent lipid spherules. Several cases of unexplained arthritis attributed to the presence of lipid spherules have been reported. Most cases were acute and involved a single joint. Positively birefringent lipid spherules have

been described as liposomes, lipid liquid crystals, smetic mesophases and fluid spherocrystal (Small, 1977; Banghan, 1980). They have a maltese cross appearance under polarized light microscopy and are spherical in shape and vary in size. Electron microscopic study of material from patients with lipid spherule arthritis has revealed the presence of lipid droplets as well as multilayered lamellated inclusions within the vacuoles of inflammatory cells (Schlesinger *et al.* 1982; Reginato *et al.* 1985; Trostle *et al.* 1986). Liquid crystals have characteristics of both liquids and crystalline solids (Small, 1977). Choi *et al.* suggested a phlogistic potential of the lipid spherules in their study because synthetic lipid microsome injected into rabbit knees induced either acute or subacute synovitis and also the numbers of liquid spherules decreased as the signs of arthritis subsided(Choi *et al.* 1986). And there were other reports for phlogistic potential of the lipid. Pritzker *et al.* demonstrated that cholesterol crystals were capable of producing a chronic synovitis (Pritzker *et al.* 1981). Intraarticular lipids may also incite the inflammatory arthritis associated with pancreatitis (Simkin *et al.* 1983). It has previously been recognized that fatty acids have chemotactic properties and that both free fatty acid and low density lipoprotein-borne lipid peroxides have cytotoxic potential (Lynn and Mukherjee, 1978; Morel *et al.* 1983).

This patient experienced acute monoarthritis in another site of his left foot one month after the first attack. In the aspirated fluid from the other site of his instep positively birefringent spherules with a maltese cross appearance were seen again under polarized microscopy. We did not test the lipid nature of spherules in this patient due to the small quantity of synovial fluid available. However, we could demonstrate indirectly the lipid nature of spherules seen in this case. In a similar period of time, a 46-year-old patient with longstanding rheumatoid arthritis (RA) who developed an acute bursitis on her left lateral malleolus was examined in our clinic. The aspirated fluid analysis revealed the presence of extracellular lipid microspherules with the same appearance of maltese crosses as was seen in the first case. Then we examined the nature of these structures. Spherules were stained positively by Sudan black and were dissolved rapidly when mixed with an equal amount of 1:1 ethanol:ether. The aspirated fluid was treated with 25mM EDTA for 24 hours at 20℃, but EDTA did not have any effect on the spherules. Therefore, we thought recurrent arthritis in different sites in our patient was attributed to positively birefringent lipid spherules. Arthritis and tendinitis in hyperlipidemic patients have been recognized as complications of hyperlipidemias. Hyperlipoproteinemia-associated arthropathy has been described with type IIa, type IV hyperlipoproteinemia. The arthritis may be acute or chronic, mono or polyarticular, and presents occasionally in a migratory pattern (Mathon *et al.* 1985), but the pathogenesis for hyperlipidemic arthropathy is not fully understood. There is evidence suggesting that the arthropathy is a true inflammatory synovitis (Glueck *et al.* 1968), is periarticular (Rooney *et al.* 1978), or that it may be induced by crystals. Crystalline cholesterol was found in joint effusions in patients with hypercholesterolemia (Zucker *et al.* 1964), and in some patients with hypertriglyceridemia and concurrent hyperuricemia the crystal concerned was almost urate (Struthers *et al.* 1983). The positively birefringent rod-like crystal was identified in a hypercholesterolemic patient with recurrent tendinitis and an achilles tendon nodule (Schumacher and Michaels, 1989). These reports showed the probability that a crystal might induce hyperlipidemic arthropathy. Rivest *et al.* first reported that lipid spherules were present in hyperlipidemic patient, who had longstanding RA and experienced acute exacerbation due to lipid spherules (Rivest *et al.* 1992). As no other reports of lipid spherules in hyperlipidemic arthropathy have yet been reported, their data deserve to be collected and to be further investigated. Our patient presented a high serum cholesterol level associated with an elevated LDL cholsterol, a type IIa hyperlipoproteinemia, and had no other causes to induce arthritis, thus the monoarthritis in our patient was thought to be related to a type IIa hyperlipoproteinemia-associated arthropathy.

The clinical characteristics featured in our case are also similar to those of several reported cases of lipid spherule-induced acute monoarthritis. Arthritis in those patients subsided within a week after the administration of non-steroidal anti-inflammatory agents or colchicine. The clinical presentation and course of lipid spherule-induced arthritis is thought to be similar to those of acute gout or other solid-

crystal-induced arthritis.

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