Fulminant gangrene in transient cold agglutinemia associated with *Escherichia coli* infection

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Fulminant gangrene of the fingers, toes and nose developed in a 57-year-old woman with *Escherichia coli* pneumonia. Cryoglobulinemia was noted, and the cryoglobulin was identified as IgM–IgG with anti-I cold agglutinin activity. The cold agglutinins possessed potent lymphocytotoxic and monocytotoxic activity and weaker granulocytotoxic activity. Treatment with plasmapheresis, steroids and antibiotics led to complete clinical recovery, although amputation of several toes was necessary. The patient died 1½ years later; the main findings at autopsy were chronic and acute pyelonephritis and acute bacterial endocarditis. This seems to be the first case of IgM–IgG cold agglutinemia occurring during the course of *E. coli* infection and the third case of fulminant gangrene complicating transient cold agglutinemia.

Une femme de 57 ans souffrant de pneumonie à *Escherichia coli* présente une gangrène fulminante des doigts, des orteils et du nez. On trouve dans son sang une cryoglobuline IgM–IgG douée d'activité agglutinine froide anti-I puissamment lymphocytotoxique et monocytotoxique et moins fortement granulocytotoxique. Le traitement par la plasmaphérèse, la prednisone et des antibiotiques permet une guérison complète, mais non sans qu'on ait dû amputer plusieurs orteils. Décès de la malade au bout d'un an et demi; l'autopsie montre principalement une pyélonéphrite aiguë et chronique et une endocardite bactérienne aiguë. Les auteurs croient rapporter le premier cas reconnu d'agglutininémie froide IgM–IgG survenu au cours d'une infection colibacillaire et le troisième cas de gangrène fulminante compliquant une telle agglutininémie transitoire.

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Transient cold agglutinemia has been described in several infectious diseases.[1] Although the condition is usually asymptomatic, severe hemolysis and vasospastic phenomena have occasionally been reported.[1] Gangrene, a very rare complication of cold agglutinemia, has been observed in some patients with persistently high titres of cold agglutinins.[2–17] Only two well documented cases of gangrene complicating transient infection-related cold agglutinemia have been reported.[18,19] We describe a patient with transient cold agglutinemia complicated by extensive gangrene during the course of *Escherichia coli* pneumonia. To our knowledge this is the first such report.

Case report

Chills, a productive cough and right-sided pleuritic pain developed in a 57-year-old woman. Over the next 2 days she experienced severe pain in and bluish discolouration of all her toes, the middle three fingers of both hands and the tip of her nose. She reported a 1-year history of a decrease in energy. Six weeks before admission to hospital she had undergone partial gastrectomy for a peptic ulcer. There was no arthralgia, Raynaud's phenomenon, dark urine, jaundice or recurrent infections. The patient was afebrile, and her blood pressure was 100/70 mm Hg, pulse rate 100 beats/min and respiratory rate 20/min. No lymphadenopathy or organomegaly was noted. A chest examination performed at the time of admission, about 4 days after the symptoms developed, gave normal results, but within 3 days decreased air entry was noted in the upper lobe of the right lung. There were no heart murmurs or bruits. She had gangrenous lesions on the tip of her nose, the distal phalanges of six fingers and all her toes. All peripheral pulses were palpable and equal. A chest x-ray film showed a patchy infiltrate in the right upper lobe, which cavitated over the next 2 days. Sputum samples repeatedly yielded *E. coli* when cultured, but blood samples remained sterile. No acid-fast bacilli were found.

The hemoglobin level was 99 g/L, the reticulocyte count varied from 3% to 8%, and spherocytes were noted in a peripheral blood smear. The leukocyte count was 10.7 $\times$ 10^9/L; neutrophils accounted for 83% and showed toxic granules. The platelet count, prothrombin and partial thromboplastin times, fibrinogen level and fibrin degradation product values were within normal limits. A direct antiglobulin test gave positive results only with C3d. Serum levels of creatinine, calcium and uric acid were within normal limits. Liver function tests and complete urinalysis gave normal results. Hepatitis B surface antigen and antibody were not found. Studies for Epstein–Barr

virus and *Mycoplasma* performed at the time of admission and during convalescence gave negative results. A bone marrow aspirate and biopsy showed granulocytic hyperplasia, with normal counts of lymphocytes and plasma cells.

Further laboratory investigations showed the following levels: total serum protein, 43 (normally 63 to 80) g/L; albumin, 16.3 (normally 35 to 52) g/L; γ-globulin, 12.4 (normally 7.0 to 16) g/L; IgG, 13.24 (normally 11.71 ± 2.55) g/L; IgA, 1.60 (normally 2.16 ± 0.86) g/L; IgM, 2.18 (normally 1.35 ± 0.61) g/L; total hemolytic complement 89.1 (normally 136 to 204) U/mL; and C3, 0.4 (normally 0.6 to 1.0) g/L. The serum viscosity was 1.2 (normally 1.1 to 1.9) mPa·s. A cryoglobulin test gave a positive result, with a cryocrit of 3% to 5%. The titre of rheumatoid factor, determined by a latex fixation test, was 1:80. The C 1 q concentration, determined by a liquid-phase C 1 q binding assay, was 13.7% (normally less than 10%). Serum immunoelectrophoresis performed at 37°C with sera against IgG, IgA, IgM, IgD, and κ and λ light chains gave normal results. Both serum and purified cryoglobulin composed of an IgM–IgG complex had strong anti-I cold agglutinin activity (confirmed by Dr. Dieter Roelcke, Heidelberg, West Germany). Both had lymphocytotoxic activity,[20] killing 78% of peripheral blood lymphocytes, 77% of B lymphocytes and 73% of T lymphocytes. Over 90% of monocytes were killed in a monocytotoxicity assay.[21] A granulocytotoxicity assay[22] showed 20% of peripheral blood granulocytes to be killed. Titres of cold agglutinins are shown in Table I. Papain- and neuraminidase-treated erythrocytes were five and four times as sensitive respectively to the patient's cold agglutinins as were untreated erythrocytes. No antibodies against neuraminic-acid-determined antigens were found by absorption with neuraminidase-treated erythrocytes. The highest temperature at which cold agglutinins were still active was 22°C.

The patient was initially treated with cefazolin, tobramycin and plasmapheresis, with 9180 mL of plasma exchanged. Afterwards sulfinpyrazone, dipyridamole and prednisone, 40 mg daily, were given. The titre of cold agglutinins dropped markedly after plasmapheresis (Table I). The gangrenous areas diminished in size, and the pain eased. However, the course was complicated by cavitation of the pneumonic areas and pneumothorax. No endobronchial lesions were shown by bronchoscopy, but bronchial washings and aspirates from the lung cavities yielded *E. coli* when cultured.

Six weeks after the onset of the gangrene, disarticulation of eight toes, including one hallux, was performed. Histologic examination of the vessels in the toes as well as of the portion of the stomach previously removed did not show any evidence of vasculitis or bacterial infection.

The patient completed 7 weeks of therapy with antibiotics. The daily prednisone dose had been gradually tapered to 10 mg. At the time of discharge, 11 weeks after admission, her hemoglobin level was 118 g/L and the cold agglutinin titres were within the normal range (Table I), but a direct antiglobulin test still gave a positive result with C3d, and lymphocytotoxic antibodies were still present, killing 57% of peripheral blood lymphocytes. A cryoglobulin test gave a negative result.

At follow-up 6 months after discharge the patient's general condition was excellent. The cold agglutinin titres were within normal limits, and a direct antiglobulin test gave a negative result.

A year and a half after the first admission the patient was admitted to another hospital with diarrhea, abdominal pain and azotemia. She died 2 weeks after admission. At autopsy the main findings were chronic and acute pyelonephritis and acute bacterial endocarditis with secondary microabscesses in the heart, spleen, brain and kidneys. Gram-positive cocci were observed in the infected areas. There was no evidence of malignant disease or vasculitis.

Discussion

Excessive synthesis of cold agglutinins may occur transiently, usually in infections, or may become persistent in proliferative B-cell diseases.[1] Cold agglutinemia is well known in conditions associated with *Mycoplasma*, Epstein–Barr virus and cytomegalovirus. In addition, cold agglutinins have been reported in influenza A and mumps and in conditions caused by adenovirus and *Legionella*.[1,23] Clinical manifestations of cold agglutinemia depend on the thermoamplitude of the cold agglutination and the degree of complement activation:[1] the higher the former and the more extensive the latter, the more severe are the expected clinical manifestations. The classic clinical syndrome consists of hemolysis and Raynaud's phenomenon.[1]

Although manifestations of Raynaud's phenomenon are common in cold agglutinemia, they almost never lead to permanent obstruction of blood vessels and gangrene. Only 17

Table I—Reciprocal titres of cold agglutinins in patient with *Escherichia coli* pneumonia and gangrene

	Temperature; titre								
	4°C			15°C			20°C		
Erythrocytes	At time of admission	After plasmapheresis	At time of discharge	At time of admission	After plasmapheresis	At time of discharge	At time of admission	After plasmapheresis	At time of discharge
Adult O	2048:1	64:1	16:1	128:1	4:1	–	4:1	–	–
Cord O	1024:1	32:1	8:1	128:1	4:1	–	–	–	–
Autologous	512:1	16:1	8:1	8:1	–	–	–	–	–

patients with persistent cold agglutinemia and gangrene have been reported.[2-17] Almost all of them had Raynaud's phenomenon, anemia and hemolysis. The thermoamplitude of the cold agglutination was high in all the investigated patients. Antiglobulin tests usually gave positive results,[7,9,11,15,16] and in four instances cryoglobulinemia was noted.[5,9,16,17] In only two instances were the cold agglutinins identified as IgMκ,[16,17] and in only two cases was the specificity reported, in one case anti-I[15] and in the other anti-i.[16]

Gangrene developing during the course of infectious, transient cold agglutinemia seems to be exceedingly rare. We found only two reported cases of acute pneumonia associated with cold agglutinemia and gangrene, both in previously healthy young women.[18,19] In neither case was bacteriologic identification of the infectious agent attempted. Ours is probably the first report of cold agglutinemia complicating *E. coli* pneumonia. Transient cryoglobulinemia was noted, and serum and purified cryoglobulin was identified as IgM–IgG with anti-I cold agglutinin activity. Immunoelectrophoretic analysis of the serum and the cryoprecipitate failed to identify a monoclonal component. Such complex cold agglutinins are very rare.[24,25] As in other patients,[20-22] the cold agglutinins in our patient had potent lymphocytotoxic and monocytotoxic activity and weaker granulocytotoxic activity.

The rapidly developing, extensive gangrene that complicated our patient's clinical course appeared to be related solely to the cryoprecipitable cold agglutinins. There was no clinical or histologic evidence of vasculitis. Whether the gangrene was related solely to the presence of cold agglutinins or to their cryoprecipitable property remains uncertain. The absence of vasculitis and of amorphous deposits in the lumen of the blood vessels makes the diagnosis of cryoglobulin-related gangrene less probable. Furthermore, given the absence of septicemia and of disseminated intravascular coagulation, the possibility that the gangrene was related to infection by gram-negative bacteria is very remote[26] (W.R. McCabe: personal communication, 1984).

Our case provides proof that cold agglutinemia may occur in infections caused by microorganisms not ordinarily associated with these antibodies and that transient cold agglutinemia may lead to fulminant gangrene.

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