

A Case of Cold Urticaria associated with Cryofibrinogenemia

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A case of cold urticaria in a 38-year-old woman was reported. The urticaria was demonstrated to have the following features:

- (i) The urticaria was associated with cryofibrinogenemia
- (ii) The passive transfer test was negative both with the patient's serum and with cryofibrinogen.
- (iii) Whereas orally administered Tavegyl was not effective, Periactin proved to be effective in the treatment of the condition.

INTRODUCTION

One of the varieties of urticaria, called physical urticaria, is caused by physical agents, e. g. mechanical stimuli, sunlight, heat and cold.^{1,2)} However, its true nature and exact pathogenetic mechanism still remain obscure and a matter of controversy.²⁾

We experienced recently a case of cold urticaria associated with cryofibrinogenemia, a relatively rare type of cold urticaria. The purpose of this paper is to present the case, with a review of pertinent literature.

CASE REPORT

About eight years before initial examination, a 38-year-old housewife began to develop erythema or wheals associated with itching over the skin areas of the face, neck, forearm or the dorsal aspect of the hands, and lower legs or dorsum pedis on exposure to cold wind in winter without known precipitating cause. These wheals disappeared in about one hour and were not accompanied by headache, abdominal pain and fever, nor by Raynaud's phenomenon and hemoglobinuria. She was entirely free from wheals during summer.

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Cold test : (1) Exposure to cold resulted in the development of erythema or wheal with itching in 5 to 10 minutes; (2) placement of a beaker containing iced water on the flexor aspect of the forearm was followed by similar skin manifestation.

Laboratory findings : Data for the following were normal; Hemoglobin, urine microscopy and analysis for blood glucose, and protein, white blood cell count and differential cell count, thrombocyte count, blood coagulation system, IgG, IgM, IgA, GOT, GPT, cholesterol, and serologic test for syphilis was negative.

Investigation of cryoprotein : The cryoprecipitate was obtained by cooling heparinized or citrated plasma for 24 hours at 4°C but negative with serum. (Fig. 1 : right, control plasma ; left, patient's plasma). This cryoprecipitate was centrifuged at 5000 rpm for 30 minutes at 4°C, washed 3 times with PBS and after being resolved in a water bath at 37°C, was subjected to immunoelectrophoresis. As illustrated in Fig. 2, the cryoprecipitate was shown to produce a precipitin line with anti-fibrinogen serum but not with anti-whole human serum. The content of the cryofibrinogen was estimated as the difference between the fibrinogen content of plasma prior to and after cooling at 4°C for 24 hours (as measured by M-Partigen-Fibrinogen).

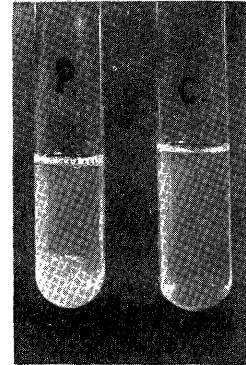


Figure. 1.

Thus, a cryofibrinogen content of 218.5 mg/dl was obtained by subtracting a post-cooling fibrinogen content of plasma of 499.1 mg/dl from a pre-cooling value of 717.6 mg/dl.

Passive transfer test : The patient's serum and cryofibrinogen were injected intradermally

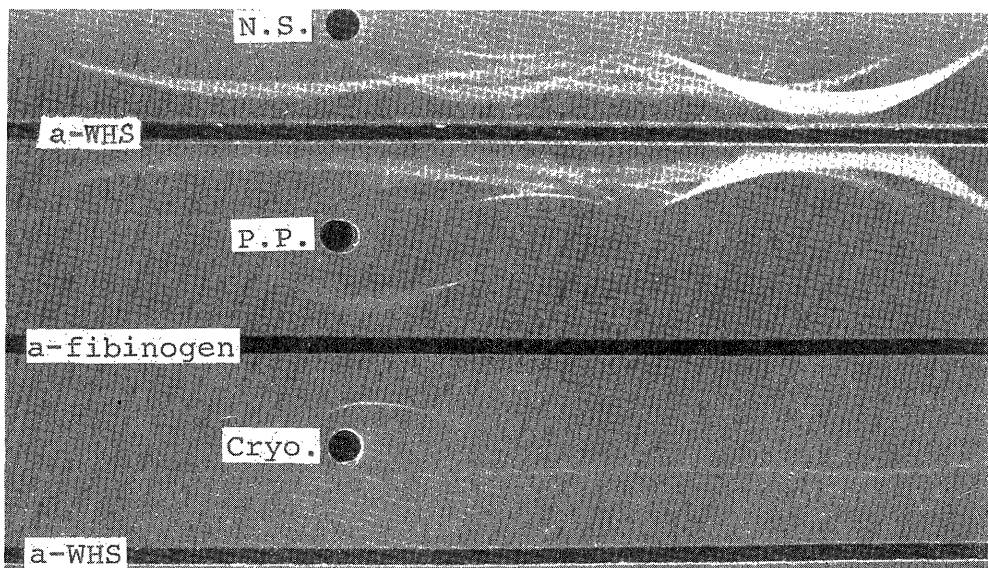


Figure. 2. N.S.; normal serum, p. p.; patient's plasma, Cryo; cryoprecipitate.

into a healthy volunteer, who was then exposed to cold 2, 6 and 24 hours after the injection. No erythema nor wheal was not seen in such treatments.

Treatment: The oral administration of Tavegyl having an antihistaminic action failed to elicit any favorable response. Periacin, which is presumed to possess antikinin action besides antihistamine and antiserotonin effects, provided adequate control of the cold urticaria. However, the patient continued to demonstrate cryofibrinogen during treatment.

DISCUSSION

Urticaria has various possible causes.^{1,2)} Cold urticaria, as indicated by statistics of Champion et al.¹⁾, is a relatively common condition in comparison with the physical variety of urticaria, such as solar urticaria. However, its pathogenetic mechanism still remains obscure in many respects.

Although there is as yet no established classification of cold urticaria,^{3,4)} the classification by Lobitz³⁾ has been frequently utilized (Tabl 1). Houser,⁵⁾ in his study of 90 reported cases, stated that of this series, 5% were congenital and familial, 67% were acquired and essential, while of the remaining 28%, 20%, 3% and 5%, respectively, were due to cryoglobulin, cryofibrinogen and cold hemolysin.

Congenital familial cold urticaria has onset at birth and is accompanied with general symptoms such as chills, fever, headache and arthralgia. It is a rare condition which is inherited as a dominant abnormality and exhibits a negative P-K reaction.^{6,7)}

The acquired essential variety accounts for the bulk of cold urticaria cases. One-third of patients with this disorder has a past or family history of atopic disease, while approximately one half gives a positive P-K reaction. In cases reported by Houser,⁵⁾ Furukawa⁸⁾ and Kaplan⁹⁾ the P-K factor was identified as IgE, while in those of Wanderer¹⁰⁾ and Ohkudo¹¹⁾ IgM was found responsible. Some allergic mechanism is thus likely to be involved in the development of cold urticaria in these cases.

Cold urticaria associated with cryoglobulinemia has been reported so far by a few

Table. 1.

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- (1) Cryoglobulinemia
 - (i) Essential Cryoglobulinemia
 - (ii) Symptomatic Cryoglobulinemia
 - (2) Paroxysmal Cold Hemoglobulinuria
 - (i) Syphilitic Paroxysmal Cold Hemoglobulinuria
 - (ii) Non-syphilitic Paroxysmal Cold Hemoglobulinuria
 - (3) Cold Hemagglutination
 - (i) Essential Cold Hemagglutination
 - (ii) Secondary Cold Hemagglutination
 - (4) Essential Cold Urticaria
 - (i) Congenital Familial Essential Cold Urticaria
 - (ii) Acquired Essential Cold Urticaria
-

authors in this country, ¹²⁾¹³⁾ but the implication of cryoglobulin in this disease state still is not known.¹³⁾¹⁴⁾

Paroxysmal cold hemoglobinuria and cold agglutininemia, conditions which are characterized by the respective presence of Donath-Landsteiner antibody and cold haemagglutinin in the serum, give rise to hemolytic manifestations and Raynaud's phenomenon on exposure to cold and may also be accompanied by cold urticaria.

Our present case was negative for P-K reaction and free from cryoglobulin and hemoglobinuria and may hence be considered to represent cold urticaria due to cryofibrinogen, a type of rare occurrence.

As can be seen in Table 2, cryofibrinogenemia may be roughly divided into 2 types, i.e. primary or idiopathic, in which a primary disease cannot be detected by any available means, and secondary which is often associated with malignant neoplasms or auto-immune diseases. Most of cases are of the latter type.¹⁵⁾

The mechanism of development of cryofibrinogenemia is controversial. Thus, some insist that cryofibrinogen is a combination product of fibrinogen denatured by a primary disease process such as malignant tumors and other blood proteins,¹⁶⁾ others surmise that cryofibrinogen might represent an intermediate product formed during the conversion of fibrinogen to fibrin in the presence of increased blood coagulability (with resultant generation of thrombin)¹⁷⁾ or a product of an antigen-antibody reaction.¹⁸⁾

Major clinical symptoms of cryofibrinogenemia are thrombosis, hemorrhage, hypersensitivity to cold and ulcer or gangrene.¹⁸⁾ Reported dermatologic manifestations include cutaneous bleeding,¹⁵⁾¹⁰⁾ cold urticaria,⁴⁾¹⁶⁾ Raynaud's phenomenon,¹⁶⁾²⁰⁾ cutis marmorata,¹⁹⁾ numbness or pain in the extremities,¹⁹⁾²¹⁾ leg ulcer²³⁾ and pyoderma gangrenosum.²⁴⁾²⁵⁾ Among reported cases of cold urticaria, one of Dagenais¹⁶⁾ was of primary cryofibrinogenemia and presented with recurrent nasal bleeding, headache and facial palsy besides cold urticaria. Cryofibrinogen in this case was demonstrated to have thrombin inhibitory effect. Miller's case,⁴⁾ too, was of primary cryofibrinogenemia with concurrent hay fever; in addition to cold urticaria, there were pain and swelling of hand joints occurring several days before menstrual flow. The author stated that whereas antihistaminics all proved of

Table 2. 2. Demonstration of Cryofibrinogenemia

I. Primary or idiopathic (with or without Raynaud's phenomenon) :
Digital gangrene, Cerebrovascular accident.
II. Secondary to :
(a) Neoplasma
Carcinoma of the buccal mucosa, Liver, Kidney, Prostate, Lung.,
Lymphoma, Multiple myeloma., Myelo-proliferative disease., Teratoma.,
(b) Collagen disease
Rheumatic fever., SLE.,
(c) Others
Ulcerative colitis., Pueumonia., Bronchiolitis., Myocardiar
infarction., Foreign body inflammation., Hyperthyroidism.,
Livercirrhosis., etc.

no therapeutic value, oral steroids were beneficial. Also in our own case the diagnosis of cold urticaria associated with primary cryofibrinogenemia was made after numerous attempts to detect a primary disease had proven unsuccessful. To be noted is the fact that the patient had no concurrent symptoms of thrombosis and hemorrhage nor did she exhibit any abnormalities in the clotting system.

The pathogenesis of this cold urticaria occurring in association with cryofibrinogenemia is entirely unknown at the present time partly because cases available are extremely few and, moreover, cold urticaria is absent in many of cryofibrinogenemia and also partly because of a lack of sufficient knowledge of cryofibrinogen. A study of additional cases will be necessary before the question of whether or not cryofibrinogenemia observed in these cases had any significance for urticaria or it represented merely a fortuitous complication of essential cold urticaria can be correctly answered.

There are a variety of substances that are supposed to act as a chemical mediator in the production of urticaria.²⁶⁾ Of particular interest is the problem of what substance or substances play such a role in the development of cold urticaria.

In this connection, Rose²⁷⁾ and Henderson²⁸⁾ noted an elevation of blood histamine level following exposure to cold. More recently, Kaplan⁹⁾ investigated 6 cases of essential cold urticaria and stated that the chemical mediator might presumably be histamine. Juhlin²⁹⁾ surmised the liberation of histamine from mast cells and basophils. Delaus³⁰⁾, on the other hand, concluded that exposure to cold is followed by release of kinin but not of histamine from his study of 11 cases. A statement to the same effect was made by Aoyama³¹⁾ in this country.

Thus, some investigators are in favor of the histamine theory, while others speak for the kinin theory. However, the facts that whereas antihistaminics produced no consistent effect, cyproheptadine which is thought to have antihistamine, antiserotonin and antikinin effects proved of therapeutic benefit³²⁾ and also that Periactin (cyproheptadine) was effective in the treatment of our present case might provide evidence in support of the kinin theory. This issue remains to be settled by further studies.

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