An Approach to the Diagnosis and Treatment of Cryofibrinogenemia

Tshering D. Amdo, MD, James A. Welker, DO

Cryofibrinogenemia is a rarely symptomatic disorder that is underrecognized due to the infrequency with which it causes symptoms. Although completely reversible, this disorder can be life threatening when untreated. In this review, the classification, pathophysiology, and clinical presentation of cryofibrinogenemia are described, based on case reports and prospective observational data. Diagnostic criteria are outlined, and therapies are assessed critically. This information should help clinicians in establishing a diagnosis of cryofibrinogenemia and initiating treatment. Am J Med. 2004;116:332–337. ©2004 by Excerpta Medica Inc.

Patients with cutaneous ulcers and gangrene have a limited differential diagnosis that includes essential cryofibrinogenemia, a rare disorder characterized by cryoprecipitation of the patients' native fibrinogen, which causes thrombotic occlusion of the small to medium arteries. When recognized early, cryofibrinogenemia is a treatable and completely reversible disease. The goal of this paper is to increase awareness of essential and secondary cryofibrinogenemia, describe a typical presentation of this syndrome, and provide an approach to diagnosis and treatment.

METHODS

Articles were obtained via a MEDLINE search, interview of two experts, and review of references obtained from articles. Searches were limited to human studies written in English. Search terms included cryofibrinogenemia, cryoprotein, plasmapheresis, and cryofiltration.

The search results yielded case reports, case series, and observational data. Due to the infrequency of symptomatic disease, there are no randomized trials. A total of 46 articles were obtained, 21 of which were eliminated due to lack of new data. All obtained articles were assessed by two reviewers who were not blinded to author, institution, or journal. Interpretation was established by consensus.

All reported treatments have been critically assessed. Treatments were considered indicated if the symptoms were relieved with the treatment, recurred with cessation of treatment, and relieved again with subsequent initiation of treatment.

CLASSIFICATION

Cryofibrinogenemia has been classified into an essential (primary) and a secondary form. Clinically relevant essential cryofibrinogenemia is rare and its prevalence is not known, although one study reported a prevalence of 3% in 135 healthy residents in Oklahoma City, Oklahoma (1). Two epidemiological studies estimated the prevalence of secondary cryofibrinogenemia in patients without symptoms of cryofibrinogenemia who were hospitalized for another illness (1,2). One study, which involved 36,000 hospitalized patients between the ages of 15 and 100 years (2), reported a prevalence of 3.4%. However, the blood samples were maintained at 4°C for only 24 hours prior to determining the presence of cryofibrinogens. In a study of 665 hospitalized patients in which samples were observed for 48 hours, the prevalence was 13% (1). Since most authors agree that the sensitivity of this assay is improved by monitoring the specimen 72 hours for cryofibrinogens, 13% is more likely to be an accurate representation of the prevalence of secondary cryofibrinogenemia.

Unfortunately, the epidemiologic data for both essential and secondary cryofibrinogenemia are quite old, and it is not known whether they are representative of patients today. Changes in the composition of hospitalized patients, such as a decreasing incidence of infectious diseases among immunocompetent patients and an increasing number of immunocompromised patients, is
expected to modify the incidence of cryofibrinogenemia. This supports the need for further epidemiologic studies.

There are limited reports suggesting a familial predilection for the disease (3–5). Presently, there seems to be insufficient information to confirm or delineate a pattern of inheritance.

**PATHOPHYSIOLOGY**

Cryofibrinogen is the term that was used by Korst and Kratochvil in 1955 to describe an abnormal, cold, precipitable protein (6). The substance is a cold, insoluble complex of fibrin, fibrinogen, and fibrin split products with albumin, plasma proteins, and immunoglobulins. Cryofibrinogen clots with thrombin and reversibly precipitates in the plasma on cooling to 4°C, then redissolves on warming to 37°C. Serum is the fluid remaining after plasma is allowed to clot. The proteins consumed in the clotting process are the necessary substrates for cryofibrinogens. Therefore, unlike cryoglobulins, which precipitate in both cooled plasma and serum, cryofibrinogens do not precipitate in cooled serum.

The pathogenesis of cryofibrinogenemia is not known. The most plausible hypothesis is based on the high plasma levels of the protease inhibitors α₁-antitrypsin and α₂-macroglobulin that have been found in patients with cryofibrinogenemia (2). These substances inhibit the fibrinolytic agent plasmin, thereby inhibiting fibrinolysis. The result is the accumulation of cryofibrinogen, which clots with thrombin and leads to the thrombotic occlusion of small and medium arteries. Additional vascular occlusion may be caused by the development of reflex vasospasm, vascular stasis, and hyperviscosity. When this occurs in end arteries, such as distal extremities, tissue ischemia and gangrene develop.

**CLINICAL PRESENTATION**

Essential cryofibrinogenemia develops spontaneously in previously healthy persons. Too few cases have been reported, however, to determine the clinical presentation by patient characteristics. Secondary cryofibrinogenemia occurs with a female to male ratio of 1.4 to 1, but with no age or racial predilection (2). These patients suffer from an underlying inflammatory disease, such as a malignancy, diabetes mellitus, collagen vascular disease, or active infection. They live in colder climates and report a temporal association between exposure to cold and the onset of symptoms. The most common symptoms are due to cutaneous ischemia, and include purpura, livido reticularis, ecchymosis, ulcerations, ischemic necrosis, and, less often, gangrene. Although any area of the body can be affected, areas that maintain a lower temperature and that are more sensitive to further cooling upon exposure to cold are more often affected. These include the hands, feet, ears, nose, and buttocks (Figure 1). Constitutional symptoms such as malaise and fever are common, and are due to the cytokine release associated with tissue ischemia and death. The presence of secondary cryofibrinogens is associated with increased mortality; however, death is not directly attributable to cryofibrinogenemia (2,7). The most directly associated cause of death is sepsis resulting from the secondary infection of gangrenous cutaneous tissue.

![Figure 1. Photograph of the feet showing edema and bullae.](image-url)
Thrombotic events occur in 25% of patients with secondary cryofibrinogenemia, irrespective of the amount of cryofibrinogen in serum (1). Although thrombotic cutaneous events are directly attributable to cryofibrinogens, the cause and effect relation of cryofibrinogens with other thrombotic events is not known. These other frequently reported thrombotic events include cerebrovascular thrombus; myocardial infarct; thrombophlebitis; obstruction of the aorta, iliac, or femoral artery; pulmonary embolus; mesenteric artery thrombosis; and retinal artery thrombosis. Similar to disseminated intravascular coagulation, paradoxical spontaneous bleeding may occur due to the depletion of clotting factors. Bleeding events have been found to be directly proportional to the amount of cryofibrinogen in serum, and have been documented in 45% of patients with heavy levels as compared with 22% of those with trace levels. The combination of thrombosis and bleeding has been only seen in 5% of patients with heavy levels (1). (The terms “heavy” and “trace” in reference to cryofibrinogen levels or concentrations are defined below in the section on diagnosis.)

Procedures that include cooling have been complicated by cryofibrinogenemia. Complications have been seen with superficial cryosurgery, cooling blankets, and the generalized body cooling that occurs during prolonged surgical procedures (5,8,9). There has been one report of dramatic complications during cosmetic superficial cryosurgery, which required the patient to undergo numerous treatments to improve the acquired facial deformity (9). The authors recommend assessing all patients for cryofibrinogenemia and testing cryosurgery on inconspicuous cutaneous locations prior to performing the definitive treatment (9).

### DIAGNOSIS

The diagnosis of cryofibrinogenemia should be considered in all previously healthy persons presenting with unexplained areas of tissue ischemia and gangrene. The differential diagnosis includes cryoglobulinemia, peripheral vascular disease, frostbite, thrombotic thrombocytopenia purpura, disseminated intravascular coagulation, coumarin necrosis, hereditary hypercoagulable states, antiphospholipid antibody syndrome, embolic diseases such as endocarditis or cholesterol emboli, vasculitis, calciphylaxis in end-stage renal disease, and purpura fulminans (Table 1).

Diagnostic criteria for essential cryofibrinogenemia have been developed based on the published literature and clinical experience (Table 2). The evidence has been divided into that which is essential and that which is supportive. The essential evidence, which is required to be present prior to making the diagnosis, includes the appropriate clinical presentation as described above, the presence of cryofibrinogens in the plasma, the absence of cryoglobulins in serum, and the exclusion of secondary causes of cryofibrinogenemia as well as other vaso-occlusive diseases. The supportive evidence is nonspecific and not compulsory, but when present along with the essential evidence, improves the accuracy of the diagnosis. These include an angiogram displaying the abrupt occlusion of small to medium arteries (Figure 2), the appropriate biopsy findings of the involved tissue as described below, and elevated serum levels of α₁-antitrypsin and α₂-macroglobulin. The diagnostic criteria for secondary cryofibrinogenemia are the same, except that the exclusion of secondary causes of cryofibrinogens is removed from the essential evidence.

The detection of cryofibrinogens requires special attention, is often done poorly by reference laboratories, and should be performed by the clinicians who suspect the diagnosis. If the sample is not centrifuged immediately, it must be kept at 37°C to prevent autoabsorption of cryofibrinogens by the red blood cells. Centrifugation that is delayed or subsequent to sample cooling leads to

### Table 1. Differential Diagnosis for Essential Cryofibrinogenemia

<table>
<thead>
<tr>
<th>Secondary cryofibrinogenemia</th>
<th>Cryoglobulinemia</th>
<th>Peripheral vascular disease</th>
<th>Frostbite</th>
<th>Thrombotic thrombocytopenia purpura</th>
<th>Disseminated intravascular coagulation</th>
<th>Coumarin necrosis</th>
<th>Hereditary hypercoagulable states</th>
<th>Embolic diseases, such as endocarditis or cholesterol emboli</th>
<th>Vasculitis</th>
<th>Calciphylaxis in end-stage renal disease</th>
<th>Antiphospholipid antibody syndrome</th>
<th>Purpura fulminans</th>
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### Table 2. Diagnostic Criteria for Essential Cryofibrinogenemia

**Essential Evidence**

- Appropriate clinical presentation: sudden onset of skin changes and constitutional symptoms, with or without thrombosis, bleeding, or exposure to cold
- Presence of cryofibrinogen in the plasma
- Absence of cryoglobulins
- No secondary causes of cryofibrinogens

**Supportive Evidence**

- Angiogram with abrupt occlusion of small to medium arteries
- Typical skin biopsy findings: cryofibrinogen plugging vessels, leukocytoclastic vasculitis, or dermal necrosis
- Elevation of serum levels of α₁-antitrypsin and α₂-macroglobulin

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discarding of cryofibrinogens with the red blood cells, and reporting of false-negative results. Blood should be collected in tubes containing oxalate, citrate, or ethylenediaminetetraacetic acid as the anticoagulant. Tubes containing heparin should not be used because of the likelihood of false-positive results due to the formation of a cryoprecipitate containing fibronectin, fibrin, and fibrinogen in combination with heparin, known as “heparin precipitable fraction” (1). After collection, the blood should be stored at 37°C until centrifuged. After centrifugation, the plasma should be stored at 4°C for 72 hours. Cryofibrinogens will develop between 24 and 72 hours after cooling (Figure 3). Cryofibrinogens can be quantitated in two ways. In the first method, “none” represents no precipitate; “heavy” indicates a precipitate greater than 100 mg percent; and “trace” indicates a precipitate present in a quantity less than 100 mg percent (1). In the second method, which refers to the approximate percent volume of plasma supernate containing precipitate, 15% to 25% equals 1+, 50% equals 2+, 75% equals 3+, and 100% equals 4+ (2). Simultaneously, a serum sample should be prepared by collecting blood in a tube free of anticoagulant, allowing the blood to clot, and then centrifuging. This serum sample should be cooled in the same manner as for cryofibrinogens to demonstrate the absence of precipitable cryoglobulins. Cryoglobulins form in both the serum and plasma, thereby hindering the ability to identify cryofibrinogens accurately and necessitating their exclusion prior to making the diagnosis of cryofibrinogenemia. In addition, Western blot analyses to purify the cryoprecipitate components suggest that cryoglobulins most likely promote the formation of cryofibrinogens. This technique demonstrates that 62% of cryofibrinogens occur in isolation, whereas 70% of cryoglobulins occur together with cryofibrinogens (10). This promotion of cryofibrinogen production indicates that treatment should be directed toward the cryoglobulins when both entities are present. Therefore, visual quantitation of precipitate accurately identifies the presence of cryofibrinogens and cryoglobulins in a manner that allows treatment decisions to be made quickly and inexpensively.

Numerous patients with cryofibrinogenemia have had to undergo skin biopsies. The most specific finding is the plugging of the superficial and deep blood vessels with thrombi containing cryofibrinogen, which stains eosinophilic with hematoxylin-eosin stain and purple-red positive with periodic acid–Schiff stain (11,12). This finding is only seen in patients with thrombotic diseases, including thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, coumarin necrosis, protein C and protein S deficiency, or monoclonal cryoglobulinemia, or the presence of lupus anticoagulant. The nonspecific findings of leukocytoclastic vasculitis and necrosis of the dermis and epidermis are more common. All of these findings are absent in asymptomatic cases of cryofibrinogenemia; when present, they are consistent with a broad differential diagnosis. This lack of sensitivity and specificity relegates histology to the status of a secondary criterion. Still, a timely biopsy can provide support for the diagnosis, and should be performed in patients in whom the diagnosis is uncertain. It is essential that the biopsy be performed prior to the development of necrosis.

The presence of elevated serum levels of α1-antitrypsin and α2-macroglobulin is less well established. These proteins were found to be elevated in a subgroup of 11 randomly selected patients with elevated plasma cryofi-
These proteins, H9251
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Figure 4. Serum protein electrophoresis demonstrating ele-
vated α2 protein levels. A/G = albumin:globulin ratio.

brinogen levels but no symptoms of the disease (2). Of
these proteins, α2-macroglobulin seems to be elevated
more frequently (13). Screening for these proteins can be
performed with serum protein electrophoresis (Figure 4).

TREATMENT

The level of the evidence on which treatment decisions
for cryofibrinogenemia are based is limited to case re-
ports. Avoidance of cold exposure and placing the symp-
tomatic patient in an environment of about 37°C is a
reasonable, inexpensive measure that is without risk, and
that has been found to be partially efficacious. Antisepsic
wound care is imperative. Cutaneous lesions should be
managed in the same way as for any gangrenous soft tis-
sue injury or burn. All patients require lifelong monitor-
ing because symptoms have a tendency to recur, espe-
cially with the cessation of therapy.

The most commonly used pharmaceutical treatments
include stanozolol, streptokinase, and steroids. A dose of
50,000 to 80,000 units of the oral fibrinolytic agent strep-
tokinase was the first reported successful treatment (12).
In patients with essential cryofibrinogenemia in whom the
diagnosis was well established, the disease was ob-
served to remit when streptokinase was administered, re-
cur when treatment was discontinued, and then remit
again when the medication was initiated. In the United
States, the oral form is unavailable; hence, streptokinase
must be administered intravenously. An intravenous
dose as low as 25,000 units and given every 24 hours
should be sufficient, since the orally administered form
does not enter the circulation in suf-
ficient amounts to produce a measurable thrombolytic effect. Based on this
evidence, streptokinase at a daily dose of either 50,000 to
80,000 units orally or 25,000 to 200,000 units intrave-
nously is indicated in the treatment of cryofibrinogen-
emia.

Stanozolol is also indicated in the treatment of cryofib-
rinogenemia. Successful treatment with stanozolol (2 to
4 mg administered orally, twice daily) has been described
in several case reports (14–17). Stanozolol has been
noted to have an onset of action of several days, which
limits its usefulness in patients suffering from an acute
onset of severe symptoms (15). As a testosterone deriva-
tive, it is an androgenic steroid that has an established
fibrinolysis-enhancing effect, which is believed to result
from its alteration of the synthesis of liver proteins in-
volved in the fibrinolytic process. However, it is associ-
ated with adverse effects, such as sodium retention, hirs-
tutism, acne, liver function abnormalities, and hyperlipidemia.

Based on the available evidence, steroids alone do not appear to be a valid treatment, but may be appropriate in
combination with immunosuppressants. The majority of
case reports do not demonstrate a beneficial effect with
high-dose steroids (10,17,18). However, reports in which
the diagnosis of essential cryofibrinogenemia was well es-
tablished demonstrated a benefit with prednisone (60
mg/d) in combination with azathioprine (150 mg/d)
(10,11), and with prednisone (10 mg/d) in combination
with chlorambucil (4 mg/d) (19). Azathioprine treatment
has been shown to be effective. In contrast, cyclophos-
phamide alone has not been shown to be beneficial (10).
Steroids should be used as needed for the treatment of an
underlying inflammatory condition (e.g., collagen vascu-
ar diseases), which can help in the control of cryofibrin-
genemia.

There is limited evidence to support the use of plasma-
pheresis. This technique was shown to be effective in one
case report in which the patient’s diagnosis was well es-
tablished (20). However, other case reports have been
complicated by the absence of cryofibrinogens in plasma
and poor outcomes (10,21,22). In one instance, a patient
had a documented decrease in cryofibrinogens, but the
cutaneous ulcers never healed and became infected, and
the patient died of sepsis (22). Several articles have sug-
gested that cryofiltration apheresis might be effective
(23–25). However, there have been no published reports
of the use of this technique in patients with cryoglobulinemia.
Furthermore, the success of other treatments vary for each of
these two diseases, and an unexpected lack of benefit of
cryofiltration apheresis has been observed in cold agglu-
tinin disease (23). At this time, plasmapheresis is a rec-
ommended treatment, whereas cryofiltration apheresis
should be considered an unproven albeit potentially ben-
eficial therapy. The cost and limited availability of these
modalities make them a second-line therapy at most hos-
pitals.
The use of heparin is not supported by the literature. Indeed, symptoms have been found to progress with use of heparin (10,19). Warfarin is potentially beneficial. Precurors to warfarin (bishydroxycoumin) have been used successfully. However, subsequent treatment with warfarin in patients with a well-established diagnosis of cryofibrinogenemia has had both successful and unsuccessful outcomes (10,18). One trial found Dextran 40 to be beneficial (18). However, it is the only report of this treatment, and neither dosage nor duration was noted. Aspirin and colchicine have been studied repeatedly and found to have no apparent benefit, and thus should not be used (10). We treated a patient with amlodipine (5 mg administered once daily), based on the principle that vasospasm may be involved in the pathogenesis of the disease, and observed that the patient’s symptoms progressed. Amlodipine is thus not recommended.

**CONCLUSION**

Cryofibrinogenemia is an underrecognized and unnecessarily life-threatening disease. The information provided in this paper should help clinicians to become more efficient at establishing a diagnosis and initiating treatment.

**ACKNOWLEDGMENT**

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**REFERENCES**