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Cryoglobulinemic vasculitis in the setting of Sjögren's syndrome: a case report and review of the literature

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Introduction

- Cryoglobulinemic vasculitis is a life-threatening disorder caused by immune complex mediated end-organ damage from precipitation and vascular occlusion of large concentrations of cryoglobulins.
- Cryoglobulins are immunoglobulins that precipitate at cold temperatures (below 37 ˚C) and redissolve with warming.[1]
- Cryoglobulinemia indicates the presence of serum immunoglobulins and are clinically classified into three types:
- Type I – *monoclonal* cryoglobulins (usually IgG or IgM)
  - Develop from gammopathies with predominant protein secretion, such as Waldenström macroglobulinemia, multiple myeloma, chronic lymphocytic leukemia, and monoclonal gammopathy of undetermined significance (MGUS)[1,2]
- Type II – a mix of *monoclonal* IgM cryoglobulins with rheumatoid factor (RF) activity and polyclonal IgG
  - Caused by infections with Hepatitis C virus (~90%), HIV, HBV, connective tissue diseases, and lymphoproliferative disorders[1–3]
- Type III – a mix of *polyclonal* IgM cryoglobulins with RF activity and polyclonal IgG[1]
  - Associated with autoimmune disorders such as Sjögren's syndrome and systemic lupus erythematosus (SLE)[1–3]
- Essential mixed cryoglobulinemia refers to ~10% of patients with cryoglobulinemia with no identifiable cause.[1]

Purpose

- In this report, we present a unique case of cryoglobulinemic vasculitis in a 48-year-old Caucasian male with Sjögren's syndrome.
- We subsequently review 9 cases of cryoglobulinemia found in the literature and provide a valuable perspective to this condition.

Background

First Hospital Presentation (5/2021):

- Progressive SOB, LLE edema, RLE wound, Raynaud phenomenon, xerostomia, urticarial rash
- CT chest/abdomen: Axillary LAD + spiculated lung lesion
- **Rheum workup**: +ANA, +SSA, +SSB, low complements, +cryoglobulins
- **Plan**: Urgent referral to Heme/Onc + Pulm, smoking cessation
  - Ordered dsDNA, Ig levels, CMV

Rheumatology appt #1 (7/2021):

- Worsening of RLE wound, continued LLE edema
- Seen by heme/onc & discussed at tumor board - not c/w malignancy
- Exam: LLE non pitting edema, hard/tender cervical adenopathy, RLE tender wound with granulation tissue and surround erythema
- **Plan**: Initiate HCQ and PDN taper 40mg → 20mg
  - Ophthalmology consult
  - Pulm visit pending

Rheumatology appt #2 (11/2021):

- CC hives (dermatology completed punch biopsy c/w LCV), resolving RLE wound
- Not taking HCQ/PDN
- Exam: Axillary LAD, left leg non-pitting edema
- Urticarial rash on arms, neck, back, abdomen + overlying excoriations
- **Plan**: Repeat CT abd/pelvis, Inguinal LN biopsy with IR, Ophtho – Schirmer and OSS
  - Established care with Tulane pulm – SABA/Stiolto, chantix
  - PFTs: Severe obstruction, moderate ↓ DLCO

Case

Third / Last Hospital Presentation:

HPI:

48-year-old previously healthy Caucasian male with recently diagnosed seropositive Sjögren's syndrome (+ANA, +SSA/SSB), cryoglobulinemia and COPD who presents with painful LLE swelling, worsening SOB, and subjective fevers.

- Social: Construction worker w/32-PY smoking history
- FamHx: Rectal cancer (father), lymphoma (maternal grandfather), no autoimmune Hx

Vitals:

- T: 97.3 F
- BP: 84/62
- HR: 116
- RR: 32
- O2 sat: 100% on 15L NRB

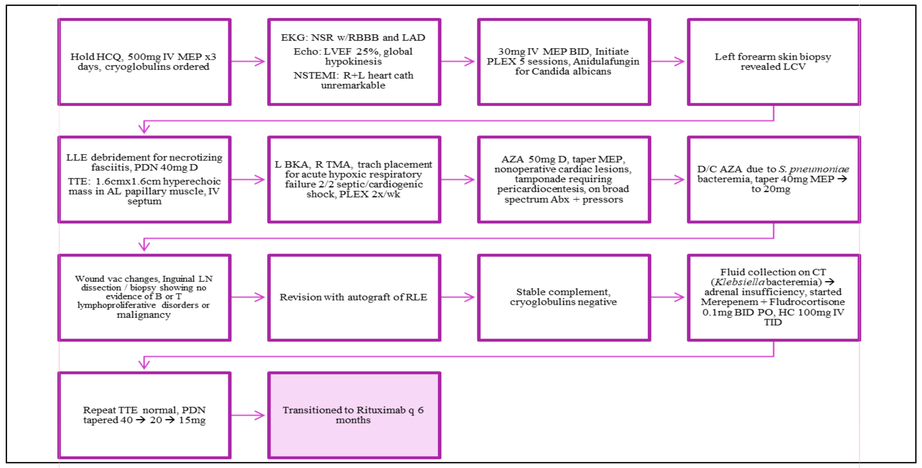
PE:

- Gen: Toxic appearing
- CV/Resp: Tachycardic, tachypneic, appears in respiratory distress
- Ext: LLE diffuse non-pitting edema, erythema, ecchymosis, & TTP

Labs:

- CBC: WBC 17.6, Hb 10.8, PT 17.6, INR 1.5
- CMP: Na 119, K 6.3, Cl 87, CO2 20, BUN 42, Cr 2.23
- LFTs: ALBUMIN 2.7, AST 221, ALT 60, ALP 116
- ESR33.8, CRP 21
- Troponin I 29.6, CK 653, BNP 603
- LDH 582, Haptoglobin 294

Hospital Course



Images

Figure A: Diffuse LLE edema upon admission

Figure B: Hospital Day 8, purpuric skin lesions, cryoglobulins ordered

Figure C: Hospital Day 11, Petechiae, R hand

Figure D: Hospital Day 11, Necrotizing fasciitis R toes

Literature review

Table 1.

Case #	Author	Year	Age/Sex	Medical History	Involved symptoms (Constitutional, Cutaneous, Arthralgias, Neuropathy, Renal, Hematologic, Vasomotor, Cardiac)	Ig and Lightchain type	Lab findings	Biopsy results	HCV status	Diagnosis	Treatment	Outcome
1	Muchtar[1]	2017	40yo M	Previously healthy	Constitutional, Cutaneous, Hematologic	Monoclonal IgM kappa	↓Hb, ↑serum viscosity	-	Negative	Type I cryoglobulinemia	PLEX (2 cycles)	Recovery
2	Muchtar[1]	2017	55yo M	Previously healthy	Cutaneous, Renal	IgM kappa	↓CH50, C3, C4, ↑Cr, RF	MPGN (renal)	Negative	WM-associated mixed cryoglobulinemia	Bendamustine-rituximab (6 cycles)	Recovery
3	Muchtar[1]	2017	62yo F	Previously healthy	Cutaneous, Renal	-	-	CD20+ k-restricted lymphocytes (BM)	Negative	Type II cryoglobulinemia	PDN, Rituximab	Resolution, relapse
4	Muchtar[1]	2017	55yo F	HCV carrier	Constitutional, Cutaneous, Arthralgias, Neuropathy	Monoclonal IgM kappa	↓C4, C3, ↑RF	-	Positive	Mixed cryoglobulinemia	PDN, Rituximab, Ribavirin, peg-IFN	Recovery
5	Muchtar[1]	2017	55yo F	CLL	Asymptomatic	Monoclonal IgG kappa	↑WBC	-	Negative	Asymptomatic cryoglobulinemia	-	-
6	Ford[4]	2019	56yo F	Chronic HCV	Constitutional, Cutaneous, Arthralgias, Cardiac	-	↓CH50, C1Q, C2, C4, ↑CRP	LCV (skin)	Positive	Cryoglobulinemic vasculitis with myocardial involvement	PDN, Glecaprevir/Pibrentasvir	Recovery
7	Thomas[3]	2020	56yo F	RA, HIV	Cutaneous, Arthralgias	-	↓C4, ↑RF, ESR, CRP	LCV (skin)	Negative	Type II cryoglobulinemia	Corticosteroids, Rituximab	Recovery
8	Reed[2]	2021	67yo F	Previously healthy	Constitutional, Cutaneous, Renal	Monoclonal IgM kappa, polyclonal IgG pattern	↓C3, C4, ↑RF, ESR, CRP, type II cryoglobulins	LCV (skin)	Negative	MALT lymphoma-associated Type II cryoglobulinemia	Corticosteroids, PLEX, Rituximab, Bendamustine	Recovery
9	VanValkenburg	2022	48yo M	SjÖgren's syndrome	Cutaneous, Arthralgias, Renal, Hematologic, Cardiac	Polyclonal IgG, IgM	↓C3, C4, ↑ESR, CRP, IgG, IgM	LCV (skin)	Negative	Mixed cryoglobulinemia	L BKA, PDN, MEP, PLEX, Rituximab	Recovery

Discussion

- Table 1 illustrates the clinical characteristics of 9 various cases of cryoglobulinemia described in the literature, including our own case.[1–4]
- The average age of patients affected with cryoglobulinemia = 54.8 years old
  - This is similar to the overall mean age of 45-60 years old at presentation among cryoglobulinemia cases previously described in the literature.[2]
- The gender distribution in our review was approximately 2:1 female:male, which is similar to the ratio of approximately 3:1 female:male previously described in the literature.[2]
- Approximately 44.5% of cases we reviewed involved previously healthy patients prior to diagnosis with cryoglobulinemia.
- Approximately 33% of patients had infectious etiologies, with 22% attributed to HCV and 11% attributed to HIV.
- Roughly 66% of patients we reviewed received corticosteroids and/or B cell depletion therapy with Rituximab, making these the two most popular treatments administered. This supports evidence from the literature that showed Rituximab given in combination with corticosteroids achieved superior clinical, renal, and immunologic responses compared to corticosteroids alone.[4]
- About 33% of patients received plasma exchange therapy due to severity of disease.
- Finally, is reassuring to note that all patients made a recovery, with 88.9% making full recovery and only 11.1% relapsing.

Conclusion/Teaching points

- **Although cryoglobulinemia has been commonly attributed to infectious etiologies such as Hepatitis C virus, our case report and brief literature review demonstrate alternative causes to keep in mind when synthesizing a differential diagnosis.**
- **Clinicians should be aware of the ever-evolving treatment options for this disease and carefully choose a tailored regimen that addresses the root cause while managing potentially life-threatening complications.**

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