The Journal of Rheumatology 2022;xx:xxxx
doi:10.3899/jrheum.220248
First Release September 15 2022

The Journal of Rheumatology

Case Report

Seronegative Polyarthritis in Association With Anti-NXP2 Antibodies: A Case Series

To the Editor:

Antinuclear matrix protein 2 (anti-NXP2) are dermatomyositis (DM)-specific autoantibodies.[1] A recent metanalysis outlined their association with muscle weakness, myalgia, dysphagia, edema, and calcinosis.[2] We report 3 cases of seronegative polyarthritis, without myositis or DM rash, attributed to anti-NXP2 autoantibodies (Table 1).

Written informed consent from study patients were obtained as part of their participation in the Canadian Inflammatory Myopathy Study. Approval by our local ethics committee (Comité d'Éthique, Centre de Recherche du CHUM, Université de Montréal) was not required for case reports with fewer than 4 patients.

Table 1. Clinical features of 3 patients with anti-NXP2 isolated polyarthritis.

	Patient 1	Patient 2	Patient 3
Sex	Female	Female	Female
Age at diagnosis, yrs	51	58	22
Ethnicity	French Canadian	French Canadian	French Canadian
Comorbidities	None	OA, hypothyroidism, fever, and abdominal pain due to CMV infection 2 months prior	ADHD, migraines
Family medical history	JIA (daughter)	Colon cancer (mother), lung cancer (father)	Unknown
Length of follow-up, months	32	11	13
Smoking	–	–	–
Muscle strength (MRC-5 scale)	5/5	5/5	5/5
Myalgia	–	–	+
Dysphagia	–	–	–
DM skin rash	–	–	–
Polyarthritis (joints)	MCP-PIP (bilateral)	PIP, wrists, ankles (bilateral)	MCP-PIP (bilateral)
Raynaud phenomenon	–	–	–
ANA (pattern)	1/640 (speckled)	1/320 (speckled)	1/640 (diffuse)
ENA	–	–	–
dsDNA	–	–	–
C3 and C4	–	–	–
aPL[a]	–	–	–
RF	–	–	–
Anti-CCP	–	–	–
Myositis panel (titer)	Anti-NXP2 (3+)	Anti-NXP2 (3+)	Anti-NXP2 (2+)
CK, IU/L (normal range 24-184)	52	34	390
CRP, mg/L (Normal < 10)	5.3	3.0	5.1
HIV screening	–	–	–
QFT	–	–	–
MRI	–	–	–
EMG	Not done	–	–
Muscle biopsy	Not done	Not done	–
Nailfold capillaroscopy	Dilated dysmorphic capillaries, no specific DM pattern	Dilated dysmorphic capillaries, no specific DM pattern	–
Cancer screening	Colonoscopy, pap smear, mammogram, abdominal US	PET scan, colonoscopy, mammogram, abdominal US CA 19-9, CA 15-3, CA 125, CEA	PET scan
IS treatment	MTX, HCQ	MTX, HCQ	Prednisone, MTX, HCQ, TOF
Status at last follow-up	Remission	Remission	Polyarthritis significantly improved

[a] aPL: anti-β_2 glycoprotein, anticardiolipin, and lupus anticoagulant antibodies. ADHD: attention deficit and hyperactivity disorder; ANA: antinuclear antibodies; Anti-CCP: anticyclic citrullinated peptide antibody; anti-NXP2: antinuclear matrix protein 2; aPL: antiphospholipid antibody; CA: cancer antigen; CEA: carcinoembryonic antigen; CK: creatine kinase; CMV: cytomegalovirus; CRP: C-reactive protein; DM: dermatomyositis; EMG: electromyography; ENA: extractable nuclear antigens; HCQ: hydroxychloroquine; IS: immunosuppressive; JIA: juvenile idiopathic arthritis; MCP: metacarpophalangeal; MRI: magnetic resonance imaging; MRC: Medical Research Council scale for muscle power evaluation; MTX: methotrexate; OA: osteoarthritis; PET: positron emission tomography; PIP: proximal interphalangeal; QFT: QuantiFERON-TB (Qiagen); RF: rheumatoid factor; TB: tuberculosis; TOF: tofacitinib; US: ultrasound.

Case 1. A 51-year-old female presented with acute polyarthritis of the hands. Examination did not show muscle weakness or DM rash. She had normal inflammatory markers and creatine kinase (CK). Serological tests demonstrated positive antinuclear antibody (ANA; 1/640 speckled) and anti-NXP2 (3+) on a myositis panel (Euroimmun). Magnetic resonance imaging (MRI) of the thighs did not show inflammatory hypersignals. Nailfold capillaroscopy showed dystrophic capillaries without a definite DM pattern. Cancer screening was negative. Her polyarthritis resolved with a short course of prednisone, followed by methotrexate (MTX) and hydroxychloroquine (HCQ).

Case 2. A 58-year-old female presented with acute polyarthritis in her hands, wrists, and ankles. Muscle strength was normal and there was no DM rash. She had normal inflammatory markers and CK. Serological tests demonstrated positive ANA (1/320 speckled) and anti-NXP2 (3+). MRI and electromyography (EMG) were normal. Nailfold capillaroscopy showed dystrophic capillaries without a specific DM pattern. Cancer screening was negative. She was successfully treated with prednisone, followed by MTX and HCQ.

Case 3. A 22-year-old female developed polyarthritis and edema in both hands. She also reported mild upper limb myalgia over the last 3 months. Examination did not reveal muscle weakness (Medical Research Council scale 5/5) or DM rash. She had normal inflammatory markers and mildly elevated CK (390 U/L, normal range 24-184). Serological tests demonstrated positive ANA (1/640 diffuse) and anti-NXP2 (2+). Muscle MRI, EMG, nailfold capillaroscopy, and quadriceps muscle biopsy were normal. Full-body positron emission tomography scan was negative. She was successfully treated with a combination of prednisone, MTX, HCQ, and tofacitinib.

In 1997, Oddis et al discovered anti-NXP2 autoantibodies, formerly named anti-MJ, in patients with juvenile DM (JDM).[3] In 2002, their target was identified as a nuclear matrix protein that contributes to RNA metabolism and nuclear architecture.[4] These autoantibodies were initially associated with a severe JDM clinical phenotype including refractory myositis, calcinosis, joint contractures, intestinal vasculitis, and polyarthritis.[5]

Our 3 cases presented with a unique phenotype of acute polyarthritis, normal inflammatory markers, and no cutaneous or muscular features of DM. We searched for articles regarding the clinical characteristics of anti-NXP2 autoantibodies (PubMed, MEDLINE, EMBASE) and summarized the data in Table 2. To our knowledge, no cases of isolated seronegative polyarthritis have been reported to date with anti-NXP2 autoantibodies. Indeed, polyarthritis has exclusively been described with concomitant myositis as reported in 2 of 4 (50%),[6] 3 of 6 (50%),[7] and all 4 (100%) cases[8] in recent case series. In 2020, Tansley et al highlighted that commercial myositis assays for anti-NXP2 autoantibodies have an excellent correlation with immunoprecipitation, the gold standard.[9] This, in addition to a positive speckled or diffuse ANA pattern, strongly exclude the issue of false positive anti-NXP2 results.

Our cases highlight that anti-NXP2 autoantibodies may present clinically with isolated seronegative polyarthritis. We suggest testing for these autoantibodies in the presence of acute polyarthritis, isolated positive ANA, and normal inflammato Although none of our patients had cancer, clinicians should remain careful as this antibody has been associated with a higher cancer risk.[10]

Table 2. Phenotype of anti-NXP2 positive myositis in the literature.

Disease entities	JDM IIM (DM > PM)
Epidemiology	Increased prevalence far from the equator zone No consistent age or sex pattern 18-25% of cases of JDM 1.6-17% of cases of IIM
Pathology	Increased capillary C5b-9 deposition Increased ischemic muscle damage
Muscle features	Severe weakness: proximal and distal Prominent myalgia and dysphagia Higher CK levels
Cutaneous features	Calcinosis, especially in JDM Distal ulcerations and edema Occasionally heliotrope and V-sign rash
Joint features	Polyarthritis described in 50-100% of myositis cases Severe arthralgias Small joints (hands and wrists) and large joints (shoulders, knees, ankles)
Systemic features	Reduced risk of ILD Increased risk of gastrointestinal vasculitis in JDM
Malignancy	Increased risk of malignancy, mostly in older males No specific association to a cancer subtype
Serology	Positive ANA (diffuse or speckled pattern) Commercial myositis assays (Euroimmun) have excellent specificity (100%) and sensitivity (84%) when compared to immunoprecipitation, the gold standard
Prognosis	No evidence of overall decreased survival Increased risk of poor treatment response Disease tends to relapse

ANA: antinuclear antibody; anti-NXP2: antinuclear matrix protein 2; CK: creatine kinase; DM: dermatomyositis; IIM: idiopathic inflammatory myopathies; ILD: interstitial lung disease; JDM: juvenile dermatomyositis; PM: polymyositis.

Aurélie Mourot[1], MD
Josiane Bourré-Tessier[2], MD, MSc, FRCPC
Valérie Nadon[3], MD
Océane Landon-Cardinal[2], MD, FRCPC
[1]Division of Internal Medicine, Centre hospitalier de l'Université de Montréal (CHUM), Department of Medicine, Université de Montréal;
[2]Division of Rheumatology, Centre hospitalier de l'Université de Montréal (CHUM), CHUM Research Center, Department of Medicine, Université de Montréal;
[3]Division of Rheumatology, Hôpital Notre-Dame, Department of Medicine, Université de Montréal, Montreal, Quebec, Canada.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. A. Mourot, Centre hospitalier de l'Université de Montréal (CHUM), 1000 Rue Saint-Denis, Montréal, QC H2X 0C1, Canada. Email: aurelie.mourot@umontreal.ca.

ACKNOWLEDGMENT

The authors would like to thank Dr. Martial Koenig for kindly reviewing the nailfold capillaroscopies of our patients.

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