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Amyloid arthropathy in smoldering myeloma: Do not take it lightly

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ABSTRACT

We report a case of smoldering multiple myeloma patient who developed signs and symptoms consistent with polyarthritis. A PET-CT demonstrated marked FDG activity in multiple joints, concerning for inflammatory arthritis. Arthrocentesis from the glenohumeral joint was consistent with inflammatory synovial fluid with no evidence for infection or crystals. Congo-red stain of the synovial fluid was positive, and mass-spectrometry based amyloid typing was consistent with wild-type transthyretin type. The patient responded instantly to glucocorticoids. This case reports highlights the feasibility of non-tissue diagnosis of amyloidosis using body fluids and underscores the importance of accurate typing to avoid erroneous treatment

1. Introduction

Systemic amyloidosis is a misfolding protein disorder leading to deposition of amyloid in organs and tissues, resulting in progressive organ function loss and ultimately death. Typically, systemic amyloidosis affects organs such as the heart, kidneys, nerves, liver and gastrointestinal tract, with organ involvement pattern largely dependent on the precursor protein [1]. However, any tissue can be involved. Reports on amyloidosis as a cause of arthritis are rare. Typically, amyloid arthropathy causes polyarthritis involving large joints. It can have an indolent course or develop into progressive arthritis[2]. Shoulder pad sign [3] has been suggested as pathognomic for AL amyloidosis. The diagnosis of amyloid arthropathy relies on the clinical presentation of arthritis with confirming amyloid deposition in joint structures, or alternatively with demonstration of amyloid in extra-articular tissue with exclusion of other causes of arthropathy. We present a case of a patient with underlying smoldering multiple myeloma who developed transthyretin (TTR) amyloid arthropathy confirmed by identifying the presence of amyloid in synovial fluid. The case report describes the diagnostic evaluation and highlights the importance of accurate typing.

2. Case report

A 77-year old man was diagnosed with IgG-lambda smoldering multiple myeloma. At diagnosis serum M-spike was 1.7 g/dL and serum free lambda 27.0 mg/dL (normal 0.57–2.63) with abnormal kappa-to-lambda ratio 0.055 (normal 0.26–1.65). A bone marrow biopsy showed 21% monotypic plasma cells. FISH showed trisomies of chromosomes 3, 7, 9 and 15. PET-CT was negative for pathological FDG uptake and/or bone lytic lesions. No criteria for therapy were met and the patient was observed for two years. He then developed severe, persistent, debilitating joint pain involving shoulders, hands, hips and knees associated with joint swelling. The pain was described as "pressure-explosive" type, was graded 5–7/10 at rest and 10/10 with activity. The pain resulted in reduced mobility, joint stiffness and poor night sleep. Physical exam revealed mild joint swelling and warmth over the symptomatic joints. Further evaluation showed normocytic anemia, hemoglobin 10.5 g/dL. Serum creatinine and calcium were normal. C-reactive protein was 44 mg/L (normal $\leq$ 8 mg/L). Rheumatoid factor and anti-CCP antibodies were negative. Serum M-spike was 1.8 g/dL and serum free lambda 31 mg/dL. A bone marrow biopsy was normocellular with 10–15% monotypic plasma cells. Congo red (CR) stain was negative for amyloid in the marrow and abdominal fat aspirate. PET-CT did not identify FDG-avid lytic lesions or plasmacytomas. However, a diffuse

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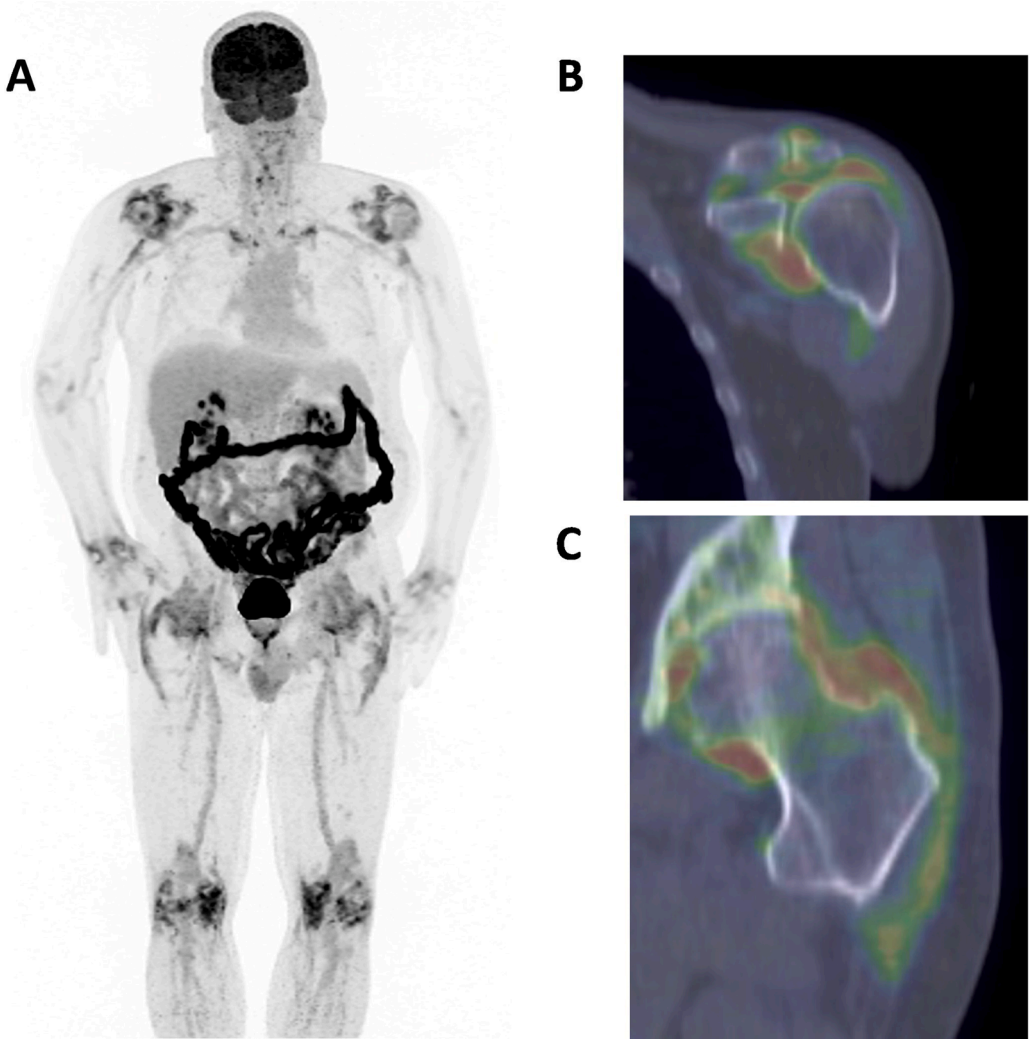


Fig. 1. FDG PET whole body maximum intensity projection (A) and fused PET and CT coronal views of the left shoulder (B) and hip (C) demonstrating diffuse, symmetric, periarticular inflammatory uptake in the shoulders, wrists, hips and knees.

symmetric large joint polyarthropathy was identified, with SUV_{max} of 7.0 at the right hip (Fig. 1). MRI of the left shoulder showed a moderate glenohumeral joint effusion with synovial thickening and mild hyperintensity on T2 weighted sequences suggesting nonspecific synovitis. There was no signs of osteoarthritis (OA) on plain x-ray or PET-CT in this patient.

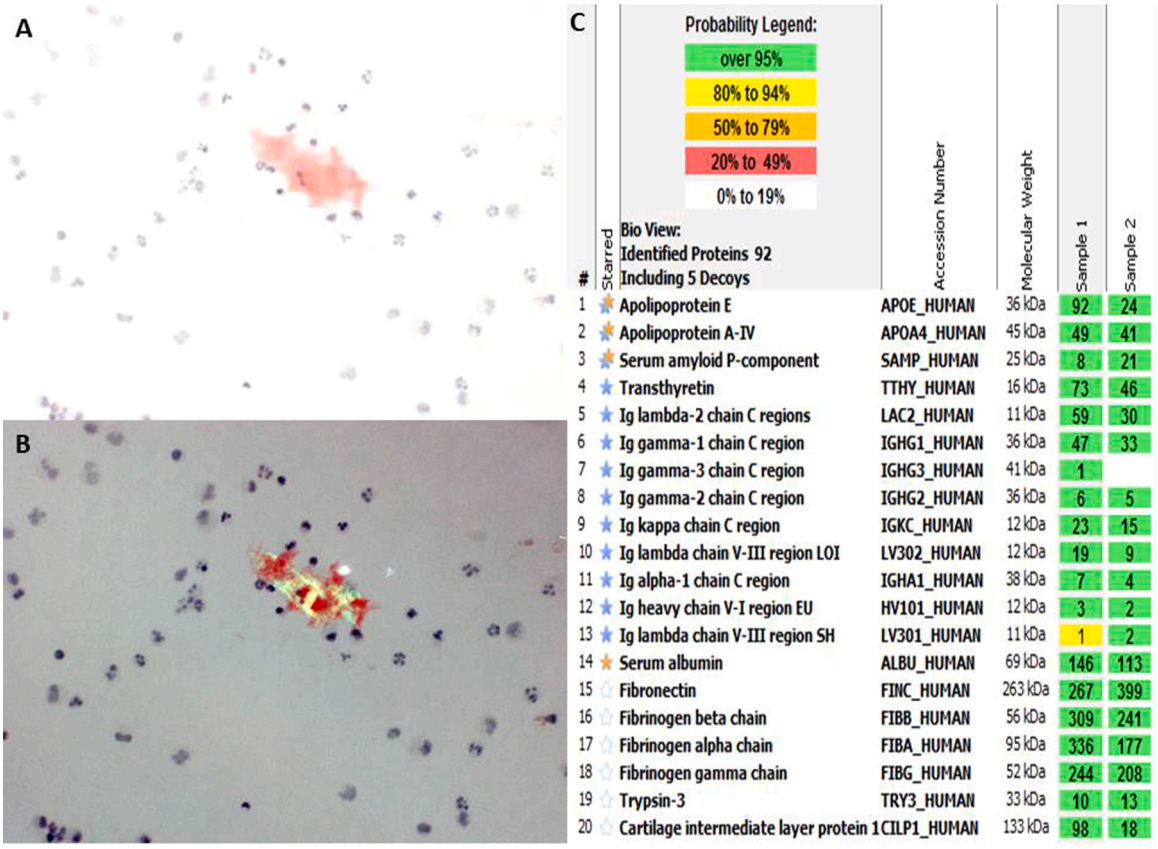
Pain management with high-dose opioids was not successful. Arthrocentesis of the left glenohumeral joint was performed. The synovial fluid was serous and contained 3944 nucleated cells\microliter, of which 50% were neutrophils. CPPD, monosodium urate crystals or malignant cells were not identified on microscopic evaluation. Synovial fluid bacterial culture was negative. A cytospins preparation of the synovial fluid was stained with CR, showing rare small fragments of CR-positive, acellular proteinaceous material showing classical apple-green birefringence under polarized light (Fig. 2A-B). A cell block was created from the fluid for the purpose of microdissection. A liquid chromatography tandem mass spectrometry analysis of the deposits detected a peptide profile consistent with TTR-type amyloid deposition (Fig. 2C)., with no amino acid sequence abnormality in the transthyretin protein, consistent with wild-type TTR. No other organ involvement with amyloid was found. Specifically, echocardiogram did not demonstrate evidence for infiltrative cardiomyopathy and PYP SPECT/CT was negative for cardiac amyloidosis.

The patient responded quickly to oral prednisone at a dose of 40 mg/d with taper. Joint swelling improved and CRP normalized within 6 weeks. However, an attempt to reduce the dose below 15 mg per day resulted in symptom flare. Diflunisal at a reduced dose of 250 mg twice a day improved symptoms control and allowed further prednisone taper.

3. Discussion

This case report illustrates two important clinical aspects. First it highlights amyloidosis as a cause of seronegative inflammatory polyarthritis. Since the diagnosis of amyloidosis requires tissue confirmation, demonstration of CR deposits is crucial for diagnosis. While CR stain is typically applied to tissue to detect amyloid deposits, it can also be applied to body fluids [4] as demonstrated in this case. Alternatively, a diagnosis of amyloid arthropathy can be made by the appropriate clinical presentation with demonstration of amyloid deposits outside the affected organ/tissue, such as fat tissue or bone marrow biopsy (both of which were negative for amyloid in this case). FDG PET-CT may be useful for identifying biopsy targets. Sensitivity for localized amyloidosis has been reported as 90%[5, 6], although sensitivity for systemic amyloidosis was poor. However, FDG PET-CT is non-specific for amyloid. A more specific amyloid tracer, ^{123}I serum amyloid P component (SAP) has been developed and is more sensitive for systemic amyloidosis [5], but has not been commercialized for general clinical use.

The second learning point is the importance of amyloid typing in



#	Starred		Accession Number	Molecular Weight	Sample 1	Sample 2
1	★	Apolipoprotein E	APOE_HUMAN	36 kDa	92	24
2	★	Apolipoprotein A-IV	APOA4_HUMAN	45 kDa	49	41
3	★	Serum amyloid P-component	SAMP_HUMAN	25 kDa	8	21
4	★	Transthyretin	TTHY_HUMAN	16 kDa	73	46
5	★	Ig lambda-2 chain C regions	LAC2_HUMAN	11 kDa	59	30
6	★	Ig gamma-1 chain C region	IGHG1_HUMAN	36 kDa	47	33
7	★	Ig gamma-3 chain C region	IGHG3_HUMAN	41 kDa	1	
8	★	Ig gamma-2 chain C region	IGHG2_HUMAN	36 kDa	6	5
9	★	Ig kappa chain C region	IGKC_HUMAN	12 kDa	23	15
10	★	Ig lambda chain V-III region LOI	LV302_HUMAN	12 kDa	19	9
11	★	Ig alpha-1 chain C region	IGHA1_HUMAN	38 kDa	7	4
12	★	Ig heavy chain V-I region EU	HV101_HUMAN	12 kDa	3	2
13	★	Ig lambda chain V-III region SH	LV301_HUMAN	11 kDa	1	2
14	★	Serum albumin	ALBU_HUMAN	69 kDa	146	113
15		Fibronectin	FINC_HUMAN	263 kDa	267	399
16		Fibrinogen beta chain	FIBB_HUMAN	56 kDa	309	241
17		Fibrinogen alpha chain	FIBA_HUMAN	95 kDa	336	177
18		Fibrinogen gamma chain	FIBG_HUMAN	52 kDa	244	208
19		Trypsin-3	TRY3_HUMAN	33 kDa	10	13
20		Cartilage intermediate layer protein 1	CILP1_HUMAN	133 kDa	98	18

Fig. 2. Cytospin preparation of synovial fluid showing Congo red-positive material (A) demonstrating apple-green birefringence under polarized light (B). Both images Congo red stain, 400x. (C) Proteomic detection of ATTR in amyloid deposits from the synovial fluid cell block. Within the boxes, the numbers represent the total number of spectra matched to the listed protein and the colors indicate the probability that the spectra represent the identified protein (only spectra with > 95% probability of a match to an identified protein [green boxes] are considered for diagnostic interpretation). There are abundant spectra for the universal amyloid proteins (APOE, SAP, and APOAIV; blue and yellow stars), providing biochemical evidence that amyloid is present in the microdissected sample. There are also many spectra corresponding to transthyretin. The somewhat elevated spectral counts for immunoglobulin lambda and immunoglobulin gamma as well as for serum albumin and fibrinogen (serum-related proteins) indicate concomitant serum contamination by the patient's known IgG-lambda myeloma (we thank Jason Theis for providing the mass spectrometry scaffold image).

order to avoid erroneous therapy. The patient had concomitant smoldering multiple myeloma, which raised the possibility of light chain amyloidosis, which is far more common as a cause of amyloid arthropathy than TTR type[2]. If amyloid typing was assumed to be light chain, then anti-plasma cell therapy could have been considered to eliminate the production of the monoclonal protein leading to amyloid formation. However, accurate typing using mass spectrometry revealed TTR thus avoiding unnecessary anti-plasma cell therapy. This case illustrates that typing with mass spectrometry can be successfully applied to amyloid deposits recovered from body fluids. Prior reports on amyloid arthropathy in the context of myeloma or other plasma cell disorders may have erroneously typed the amyloid as light chain using less accurate typing methods than currently available. SMM and ATTR amyloidosis are distinct of each other, although higher percentage of plasma cells disorders, mainly monoclonal gammopathy of undetermined significance, have been reported in patients with wild-type ATTR amyloidosis[7-10].

There are several case reports and case series on amyloid arthropathy, mostly with light chain or β2-microglobulin type. TTR amyloid in joint tissue has been rarely reported, mostly as an incidental finding in patients with OA[7-12], both diseases of the elderly. Hip or knee arthroplasty was more common in ATTR amyloidosis than expected and preceded the diagnosis of ATTR amyloidosis by an average of 7 years [13]. Although the detection of amyloid deposits in the synovial fluid may be an incidental finding, as no other cause of arthritis was evident and as amyloidosis is an established cause of arthritis support our assumption that amyloidosis was the underlying cause for the inflammatory arthritis. It is noteworthy that the PET-CT showing diffuse and symmetrical FDG uptake in multiple joints is very suggestive for inflammatory arthritis, rather than OA. Our patient also lacked significant imaging findings to suggest OA. We recommend considering adding Congo Red staining to synovial fluid in seronegative inflammatory arthritis. This would help to assess the prevalence of amyloid arthropathy in this patient population, which is thought to be low, but may be underdiagnosed. Our experience does not support a routine more invasive approach, such as cartilage biopsy, for diagnostic evaluation of amyloid arthropathy.

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Declaration of Competing Interest

AD reports scientific board advisory participation for Alnylam, Intellia and Janssen and grants from Takeda, Pfizer, Prothena, Celgene, Alnylam and Janssen. MAG reports consultancy for Millennium Pharmaceuticals and received honoraria from Celgene, Millennium Pharmaceuticals, Onyx Pharmaceuticals, Novartis, GlaxoSmithKline, Prothena, Ionis Pharmaceuticals, and Amgen. The remaining authors declare no competing financial interests.

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