Amyloid arthropathy in smoldering myeloma: Do not take it lightly

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https://doi.org/10.1016/j.lrr.2021.100242
Received 20 March 2021; Received in revised form 9 April 2021; Accepted 21 April 2021
Available online 24 April 2021
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ARTICLE INFO

Keywords:
Amyloidosis
Arthropathic
Amyloidosis
Congo red

ABSTRACT

We report a case of smoldering multiple myeloma patient who developed signs and symptoms consistent with polyarthritits. 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 report 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 arthropathy causes polyarthritis involving large joints. It can have an indolent course or develop into progressive arthritis [2].

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 ≤ 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...
Symmetric large joint polyarthropathy was identified, with SUV\textsubscript{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/μl, 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. 2 A-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/day 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, \textsuperscript{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
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.

Funding
None

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

Eli Muchtar designed the study, performed the research, analyzed the data, drafted the paper and approved the final version of the manuscript; Rebecca L. King analyzed the data, provided pathological images, revised the manuscript and approved its final version; Ellen D. McPhail analyzed the data, provided pathological images, revised the manuscript and approved its final version; Matthew P. Thorpe analyzed the data, provided radiological images, revised the manuscript and approved its final version; Wilson Gonsalves analyzed the data, revised the manuscript and approved its final version; Floranne Ernste analyzed the data, revised the manuscript and approved its final version; Martha Grogan analyzed the data, revised the manuscript and approved its final version; Angela Dispenzieri analyzed the data, revised the manuscript and approved its final version; Morie A. Gertz performed the research, analyzed the data, performed the first manuscript revision, and approved the final version of the manuscript.

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