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Amyloid arthropathy associated with multiple myeloma: A systematic analysis of 101 reported cases

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ABSTRACT

Objective: Amyloid deposition in multiple myeloma (MM) may lead to an arthropathy resembling rheumatoid arthritis (RA). Since a systematic description of its natural history is lacking, we have performed a systematic analysis of all published cases.
Methods: Literature review featuring backward and forward database searches and direct inspection of reference lists. Inclusion criteria were as follows: publication between 1931 and 2012, diagnosis of multiple myeloma, and demonstration of light chain amyloid (AL) in any organ or in synovial fluid, arthritis, or synovitis.
Results: Overall, 101 cases were identified. Median age was 59 years and the male-to-female ratio was 1:1. A systemic manifestation of MM was reported in 88 cases. In 53 of these, characteristic physical findings (carpal tunnel syndrome, macroglossia, shoulder pad, and soft tissue swelling/masses) were present. Arthritis manifested before the diagnosis of MM in 63 cases, with 33 cases initially misdiagnosed as RA. There were 72 cases of poly-, 17 of oligo-, and three of monoarthritis. The shoulder joint was most commonly affected, followed by knees and small hand joints. Median synovial fluid leukocyte count was 2460 cells/mm^3, and was normal in seven cases. Synovial histopathology often featured mild synovitis without plasma cell infiltration. Imaging revealed articular or periarticular inflammation in many cases and bone lesions near 22% of affected joints. Treatments varied but led to some improvement in the majority of cases.
Conclusions: These results solidify previous experience that MM arthropathy tends to feature a symmetric RF-negative nonerosive polyarthritis. However, the results also highlight the diversity of its presentations and stress the importance of arthropathy as a potentially under-recognized presenting manifestation of MM.

Introduction

Deposition of immunoglobulin (Ig) light chains may lead to amyloidosis in diverse organs. The most common causes are monoclonal gammopathies, accounting for about 70% of cases, followed by multiple myeloma (MM) (20%), and Waldenström's macroglobulinemia

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(10%) [1]. Of these, MM leads to the most severe pathology. It is therefore most critical to recognize it as the underlying systemic disease if amyloidosis is a presenting feature. Synovitis may result when MM-associated light chain amyloid (also referred to as AL amyloid) deposits form in the joints. The clinical presentation of this MM-associated amyloid arthropathy (MAA) often resembles RA [2], and it is important to differentiate between the two entities since treatments differ and recognition of multiple myeloma as an underlying malignancy is essential. MAA has been the subject of small case series and individual case reports, and its incidence in MM has been estimated between 3.7% and 9.2% [3,4], but a unifying analysis of its clinical and laboratory features is not available. We have therefore performed a comprehensive analysis of the international literature on MAA and have attempted to identify features that can be used to differentiate it from RA. While confirming results from smaller case series that MAA is a symmetric nonerosive polyarthritis, our analysis unveils several hitherto underappreciated aspects, including oligo- and monoarticular presentations, the shoulder as the most frequently affected joint, the presence of joint erosions in a subset, and that articular manifestations precede the diagnosis of MM in the majority of cases.

Methods

Literature search

The literature search was conducted according to the guidelines for systematic reviews [5]. PubMed and Google scholar were searched using the key words *amyloid* OR *amyloidosis* AND *myeloma* OR *myelomatosis* AND *arthritis* OR *arthropathy* OR *synovitis*. Forward searches were conducted with Google Scholar using references [6,7] as root publications. The Chinese National Knowledge Infrastructure (CNKI, available at www.cnki.net) was searched by one of the authors (L.D.), who is a native speaker of Mandarin. The reference lists of all publications that met entry criteria were searched for additional reports. All cases meeting the following criteria were included in the analyses: (1) diagnosis of multiple myeloma based on biopsy (e.g. bone marrow biopsy and aspiration and other tissue biopsies), (2) diagnosis of amyloidosis based on synovial or other tissue biopsies, (3) arthritis or synovitis, and (4) publication between January 1, 1931 and December 31, 2012. Two new cases well known to the authors [8] were also included. Cases of amyloidosis due to causes other than MM were not considered.

Results

Literature search

Approximately 650 publications were screened. The PubMed and Google Scholar backward searches yielded 446 publications to be screened, in which 80 cases fulfilled inclusion criteria. The CNKI search yielded two cases and the Google Scholar forward search yielded an additional 11 publications containing a total of 11 cases. Inspection of the reference lists yielded an additional four publications containing a total of eight cases. Thus, 63 publications containing 99 cases were identified. Together with the two unpublished cases, 101 cases were thus available for subsequent analyses. All articles met criteria for evidence level 4 according to the University of Oxford Centre for Evidence-Based Medicine grading scheme [9]. There were no articles of level 3 or better. Twenty-one publications (33%) were from the USA, eight (24%) from France, six (9.5%) from the UK, four (6.3%) from Japan, three (4.8%) each from Canada, China, and Turkey, two (3.8%) each from India and Spain, and one (1.6%) each from Australia, Austria, the Czech Republic, Denmark, Germany, Greece, Iran, Israel, Mexico, the Netherlands, and Tunisia. The reports were authored by a variety of clinical specialists. In the 42 reports where first and senior author had the same specialty or only one author was listed, 22 reports (52%) were published by rheumatologists, eight (19%) by pathologists, five (12%) by radiologists, two (5%) by hematologists, and one (2%) each by immunologists, nephrologists, "amyloid treatment specialists," orthopedists, and orthopedic surgeons. Additional nine reports were published from departments of internal medicine without a specified subspecialty. In the remaining 12 reports, the first and senior authors came from two different specialties, comprising pathology (n = 7; 30% of the 24 first and senior authorships), rheumatology (6; 25%), hematology (3; 12.5%), epidemiology

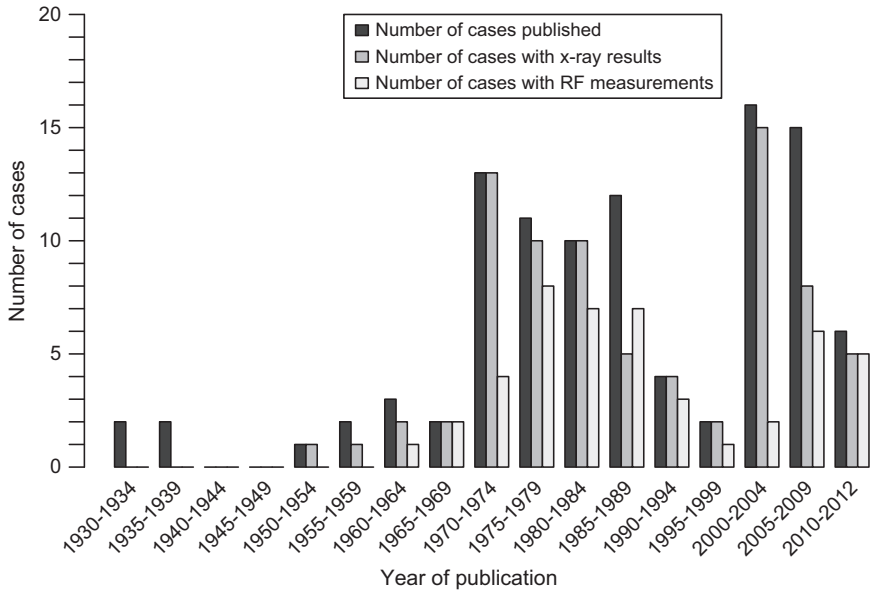

Fig. 1. Temporal distribution of reports of MAA since 1931. (A) Number of cases (y-axis) published in 5-year intervals (x-axis). Dark gray bars, number of cases; medium gray bars, number of cases in which results of plain radiographs were reported; and light gray bars, number of cases in which RF status was reported.