

Atlanto-axial Pannus in Patients with and without Rheumatoid Arthritis

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ABSTRACT. Objective. Pannus formation in the atlanto-axial joint is a well-recognized complication of rheumatoid arthritis (RA). Occasionally, atlanto-axial pannus is reported when patients without a history of RA undergo magnetic resonance imaging (MRI) of the cervical spine. We sought to further characterize these patients.

Methods. The Partners HealthCare Research Patient Data Registry was free-text searched for “atlanto-axial” AND “pannus” in cervical spine MRI reports from 2001 to 2015. Cases with MRI reports describing pannus were reviewed. Clinical data were extracted by chart review in cases with confirmed atlanto-axial pannus (n = 105).

Results. Twenty-nine patients (27.6%) had RA, all of whom except one carried this diagnosis at the time of the MRI scan. Only 1 of 77 patients without a history of RA was subsequently diagnosed with RA (1.3%, 95% CI 0.1–7.0%, median followup 3.6 yrs). Non-RA patients were significantly older (median age 79 vs 63 yrs, $p < 0.0001$), less frequently female (55% vs 86%, $p = 0.0032$), and more likely to have undergone prior cervical spine surgery (18% vs 0%, $p = 0.016$) compared with RA patients. Thirty-four non-RA patients (44.7%) either had a clinical diagnosis of calcium pyrophosphate dihydrate disease (CPPD) or imaging evidence for tissue calcification. There were no significant differences in age or sex between the CPPD subgroup and other non-RA patients. Twenty-eight patients (26.7%) underwent cervical spine surgery.

Conclusion. Patients without RA diagnosis and incidental atlanto-axial pannus on cervical spine MRI are unlikely to have previously unrecognized RA. Degenerative disease and tissue calcification may contribute to pannus formation in these patients. (First Release August 15 2019; *J Rheumatol* 2019;46:1431–7; doi:10.3899/jrheum.181429)

Key Indexing Terms:

ATLANTO-AXIAL JOINT SPINE CHONDROCALCINOSIS RHEUMATOID ARTHRITIS

The term *pannus* (cloth, Latin) is used in several medical contexts. While pannus of the eye refers to a vascularized tissue invading the cornea in patients with trachoma, abdominal pannus describes the skin apron in morbidly obese patients^{1,2}. In rheumatology, pannus refers to an aggressive structure in the inflamed rheumatoid joint that invades cartilage and bone, thereby causing irreversible joint damage³. It is well established that pannus involving the atlanto-axial joint in rheumatoid arthritis (RA) can lead to instability and spinal cord injury due to compression of the cervico-medullary junction^{4,5,6}.

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While most commonly associated with RA, the term *pannus* has also been used to describe retro-odontoid soft tissue masses in patients with calcium pyrophosphate dihydrate disease (CPPD)⁷, juvenile idiopathic arthritis (JIA)⁸, and spondyloarthritis (SpA)^{9,10}, consistent with a primary role of inflammation in the pathogenesis of these conditions. Others have noted pannus-like lesions in patients with severe degenerative disease in the cervical spine^{11,12}, and it has been suggested that instability might be the driver rather than a consequence of pannus formation in the atlanto-axial joint¹³. Indeed, surgical fusion of the C1/C2 junction has been shown to result in regression of pannus tissue on repeat imaging^{14,15,16}.

We report here the results of a retrospective analysis of 105 patients with pannus in the atlanto-axial joint. Cases were identified by free-text searching of radiology reports of cervical spine magnetic resonance imaging (MRI) studies. Less than one-third of the patients had RA, while degenerative spine disease and evidence for tissue calcification were common.

MATERIALS AND METHODS

Case identification. Our study was approved by the Partners HealthCare Institutional Review Board (IRB# 2016P001601). Partners HealthCare is an

integrated not-for-profit healthcare system that includes Brigham and Women's Hospital, Massachusetts General Hospital, and other hospitals and institutions in Boston, Massachusetts, USA. The Partners HealthCare Research Patient Data Registry (RPDR)¹⁷ is a repository of clinical data from electronic medical record (EMR) systems of Partners HealthCare-affiliated institutions. We searched the RPDR for MRI studies of the cervical spine performed in patients 18 years or older between January 1, 2001, and December 31, 2015. The radiology reports for these studies were free-text searched using the terms "atlanto-axial" (or "atlantoaxial") and "pannus," yielding 171 hits. MRI reports were retrieved and a single investigator (AAJ) read all MRI reports to exclude those that mentioned "no pannus" or used similar language to describe the absence of pannus. A total of 117 records had MRI reports documenting "definite" or "possible" pannus in the atlanto-axial joint. For patients with multiple MRI studies, the earliest study with identified pannus was considered as the index MRI and analyzed further.

MRI review. The original MRI studies were retrieved and 2 radiologists (JCM, an attending musculoskeletal radiologist with 4 years of experience, and JS, a postgraduate radiology resident in yr 3) independently reviewed all cases using the following working definition for pannus: "non-fluid signal intensity material either extending beyond the anterior, posterior, or superior cortical margins of the dens, or erosive changes of the dens filled-in with nonfluid signal intensity material." Of the 117 cases, 2 cases could not be reviewed because the images were not available; a third case was excluded because the report mentioning pannus referred to a brain MRI study and the cranio-cervical junction was only partially imaged. Thus, a total of 114 cases were reviewed. In 73 cases, the clinical radiologist reading the study unambiguously reported the presence of pannus ("definite pannus"). The other 41 reports described the presence of pannus using qualifiers such as "suggestion of," "in keeping with," or "possible" and were thus classified as documenting "possible pannus." The MRI studies were de-identified and reviewed in a random order. Each reader was blinded to age, sex, clinical diagnoses, as well as original pannus classification ("definite" vs "possible"). T1-weighted, T2-weighted, and fluid-sensitive (either short-tau inversion recovery or T2-weighted with fat suppression) sequences were evaluated, although there was some heterogeneity between studies regarding acquired sequences. No cases were excluded based on technical factors such as motion artifacts or incomplete examinations; image quality was deemed adequate by both readers for all cases.

Data extraction. For all subjects with confirmed pannus, clinical data were extracted by chart review of EMR data. Each chart was reviewed to determine whether there was a diagnosis of RA on the problem list, any history of positive rheumatoid factor or anticyclic citrullinated peptide antibody, or "rheumatoid" mentioned in EMR notes. If any of these criteria were met, the chart was reviewed by a rheumatologist (JE) to confirm the diagnosis of RA. Similarly, each chart was screened to determine whether there was a diagnosis of CPPD or pseudogout on the problem list, or if the terms "CPPD," "pseudogout," "chondrocalcinosis," or "crowned" were mentioned in any EMR notes. If any of these criteria were met, the chart was then reviewed to determine whether the patient had a clinical diagnosis of CPPD or whether chondrocalcinosis was an incidental imaging finding. For patients who had undergone computed tomography (CT) scanning of their cervical spine at any time, the images were retrieved and reviewed for the presence of calcification in the atlanto-axial joint. Additionally, each chart was reviewed for the presence of other inflammatory rheumatic conditions by reviewing the problem list, by searching for the terms "arthritis," "gout," "SLE [systemic lupus erythematosus]," and "lupus" in EMR notes, and by reviewing the most recent note written by a rheumatologist, if one was present.

Charts were further reviewed for neurological symptoms or signs at the time of the index MRI that likely triggered the imaging study. Findings were classified into 4 categories: neck pain, radicular pain or headache, upper extremity motor or sensory deficit, and neurologic findings indicating cervical myelopathy. Radicular pain was defined as pain radiating to the shoulders, arms, or head. Headache was grouped with radicular pain, as

impingement of the upper cervical nerve roots may cause headache. Upper extremity motor or sensory deficits included any subjective or objective deficits such as numbness, tingling, reduced sensation, weakness, or hyporeflexia. Myelopathic symptoms and signs included new findings of any of the following: gait impairment, impaired balance, recurrent falls, bilateral upper extremity weakness, hand clumsiness, dyscoordination, concurrent upper and lower extremity weakness, and hyperreflexia. Any trauma preceding the index MRI was noted. In cases in which signs or symptoms were not reported, the data were coded as missing and excluded from statistical analyses.

For patients who underwent surgery of the cervical spine, the dates and types of surgery were extracted from operative notes. Operative notes were reviewed to determine whether the surgery involved the atlanto-axial region. Based on available literature, these were considered surgeries involving the atlanto-axial region: occipito-cervical fusion, C1-C2 fusion, posterior fossa craniectomy, pannus resection, and odontoid resection^{14,18,19}.

Statistical analysis. Baseline characteristics between groups were compared using the Wilcoxon rank-sum test for age and chi-square test for categorical variables. The Wilcoxon rank-sum test was used for age because this variable was not normally distributed. For the categories of race, prior cervical spine surgery, and specialty providing referral for MRI, Fisher's exact test was used given very small sample sizes in some categories. We set $\alpha = 0.05$ to determine statistical significance, and all p values were 2-sided. The 95% CI was calculated using the Wilson/Brown method. Data were analyzed using SAS 9.4 and Prism 7 (Graphpad).

RESULTS

Confirmation of atlanto-axial pannus. By free-text searching the EMR of our hospital network, we identified 114 cases with "definite" or "possible" pannus mentioned in the radiology report of a cervical spine MRI study and images available for review. After the 2 radiologists independently reviewed the original MRI scans in a blinded manner, 100/114 (87.8%) studies were determined by both readers to be positive for pannus, 2/114 (1.8%) were concordantly read as negative for pannus, and 12/114 (10.5%) were discrepant between the 2 readers. The discrepant cases were reviewed in an additional reading session to arrive at a consensus interpretation, which resulted in classification of 5/12 as positive and 7/12 as negative for pannus. Thus, 105/114 (92.1%) cases were ultimately considered positive for atlanto-axial pannus (Figure 1) and analyzed further.

Patients with RA. Chart review revealed that 29/105 (27.6%) patients with confirmed pannus in the atlanto-axial joint had RA. Representative MRI images are shown in Figure 2. All except 1 patient carried the RA diagnosis at the time of the index MRI. Baseline characteristics of RA patients and non-RA patients are compared in Table 1. Patients with RA were significantly younger (median age 63 yrs, IQR 49–71 yrs) than non-RA patients (median age 79 yrs, IQR 72–85 yrs; $p < 0.0001$) and more frequently female (86% vs 55%, $p = 0.0032$). Patients with RA were also more frequently referred for MRI evaluation by a rheumatologist (62% vs 4%, $p < 0.0001$) and less likely to have a history of prior cervical spine surgery (0% vs 18%, $p = 0.016$). There were no differences regarding race or indication for cervical spine imaging. Median disease duration in the patients with RA was 19 years (IQR 6–69 yrs), and 73% (19/26 patients with available data)

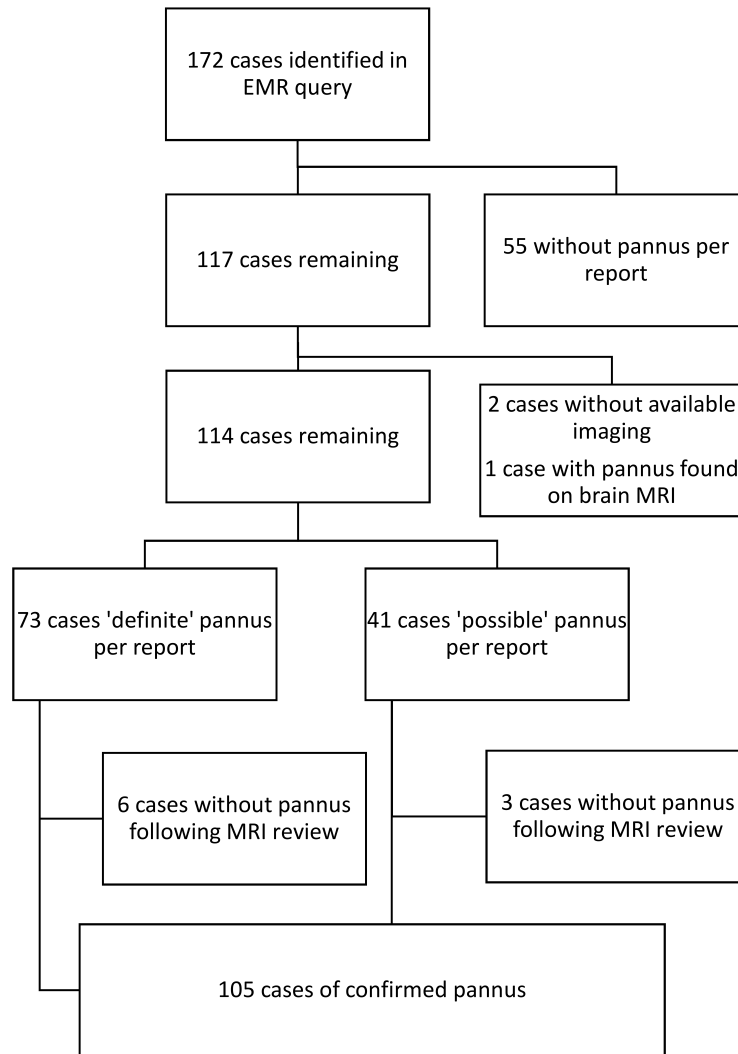


Figure 1. Flowchart showing the identification of cases with confirmed atlanto-axial pannus. EMR: electronic medical record; MRI: magnetic resonance imaging.

were seropositive. Nineteen out of 29 (66%) patients with RA were receiving biologic therapy prior to the index MRI.

Non-RA patients. EMR data were available for a median 3.6 years (IQR 2.3–6.6 yrs) following the index MRI. Only 1 patient without preexisting RA diagnosis was subsequently diagnosed with RA (1/77, 1.3%, 95% CI 0.1–7.0%). Looking for other inflammatory rheumatic diseases, we found that 9/76 (11.8%) patients had a clinical diagnosis of CPPD and 23/76 (30.2%) had chondrocalcinosis on radiographs of peripheral joints. Excluding subjects without informative imaging studies (i.e., at least 1 radiograph of hand/wrist, hip/pelvis, or knee)²⁰, 23/53 (43.4%) had chondrocalcinosis in peripheral joints. Forty-eight out of 76 patients had a CT scan of the cervical spine at any timepoint, in which 29 cases (60.4%) demonstrated calcifications in the atlanto-axial joint. A representative example is shown in Figure 3. Together,

34/76 patients (44.7%) had either a clinical diagnosis of CPPD or imaging evidence of tissue calcification in the atlanto-axial joint or elsewhere. This CPPD group did not differ from the remaining 42 non-RA patients regarding demographic variables (Table 2). We did not identify any large clusters of other inflammatory rheumatic diseases, although a few patients were noted to have JIA (n = 1), SLE (n = 1), gout (n = 3), or SpA (n = 1).

Spine surgery. In total, 28/105 patients (26.7%) underwent surgery of the cervical spine after the index MRI demonstrated atlanto-axial pannus (Table 3). Of those undergoing surgery, 4/28 (14.3%) had a fracture of the atlas or dens, compared with 7/75 (9.3%) who did not undergo surgery (p = 0.4714). Surgery was performed a median of 38 (IQR 6.5–93) days after the index MRI. There was a trend that patients who underwent surgery had upper extremity neuro-

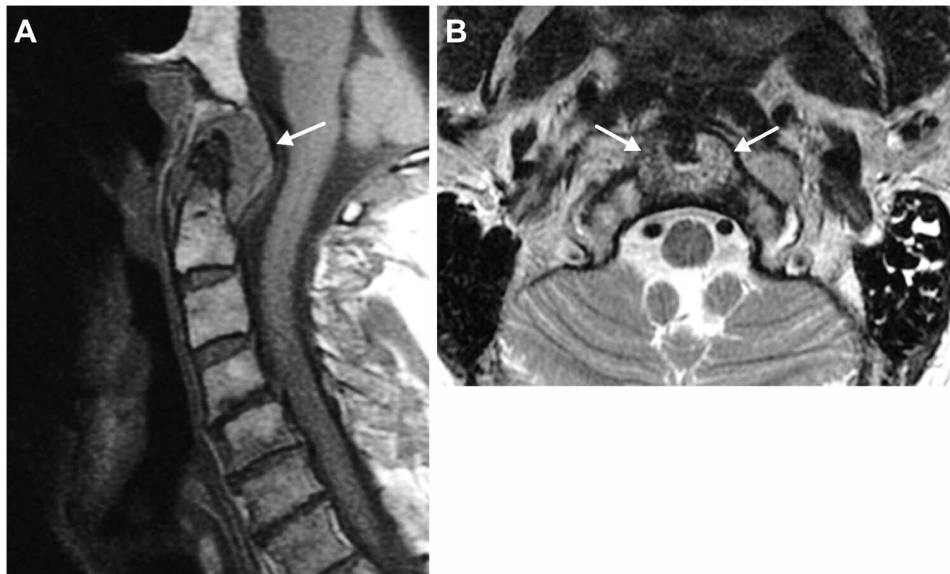


Figure 2. Atlanto-axial pannus in a 68-year-old male with a 6-year history of seropositive RA. (A) Sagittal T1-weighted MRI image demonstrating a soft tissue mass (arrow) surrounding the odontoid process with mass effect on the thecal sac and spinal cord. There is associated bony erosion and abnormal marrow signal. (B) Axial T2-weighted MRI image from the same patient showing the soft tissue mass (arrows) in the axial plane. MRI: magnetic resonance imaging.

Table 1. Characteristics of patients with atlanto-axial pannus.

Characteristics	Total, n = 105	RA, n = 29	No RA, n = 76	p
Age, yrs, median (IQR)	75 (65–83)	63 (49–71)	79 (72–85)	< 0.0001
Sex				0.0032
Female	67 (64)	25 (86)	42 (55)	
Male	38 (36)	4 (14)	34 (45)	
Race				0.49
White	87 (85)	22 (79)	65 (88)	
Hispanic	4 (4)	2 (7)	2 (3)	
Asian or Pacific Islander	3 (3)	1 (4)	2 (3)	
Black	8 (8)	3 (11)	5 (7)	
Pertinent clinical history				
Neck pain	69 (78)	22 (81)	47 (76)	0.56
Radicular pain or headache	37 (51)	9 (39)	28 (57)	0.15
Upper extremity motor or sensory deficit	36 (42)	11 (39)	25 (43)	0.74
Findings of myelopathy	36 (39)	12 (43)	24 (37)	0.59
Trauma	27 (26)	4 (14)	23 (32)	0.07
Prior cervical spine surgery	12 (13)	0 (0)	12 (18)	0.016
Cervical spine surgery after index MRI				
Any cervical spine surgery	28 (27)	6 (21)	22 (30)	0.35
Surgery of atlanto-axial region	17 (17)	4 (14)	13 (15)	0.78

Values are n (%) unless otherwise specified. Percentages were calculated excluding subjects with missing data. Values in bold face are statistically significant. RA: rheumatoid arthritis; IQR: interquartile range; MRI: magnetic resonance imaging.

logical deficits ($p = 0.07$) or myelopathic symptoms or signs ($p = 0.14$) more frequently, and neck pain ($p = 0.13$) or radicular pain ($p = 0.15$) less frequently than conservatively managed patients.

Of those managed surgically, 17/28 patients (60.7%)

underwent surgery involving the atlanto-axial region. There were no significant differences in age, sex, race, or symptomatology between those who had surgery involving the atlanto-axial region and patients who had surgery of more caudal cervical spine levels. Surgical rates of the atlanto-axial

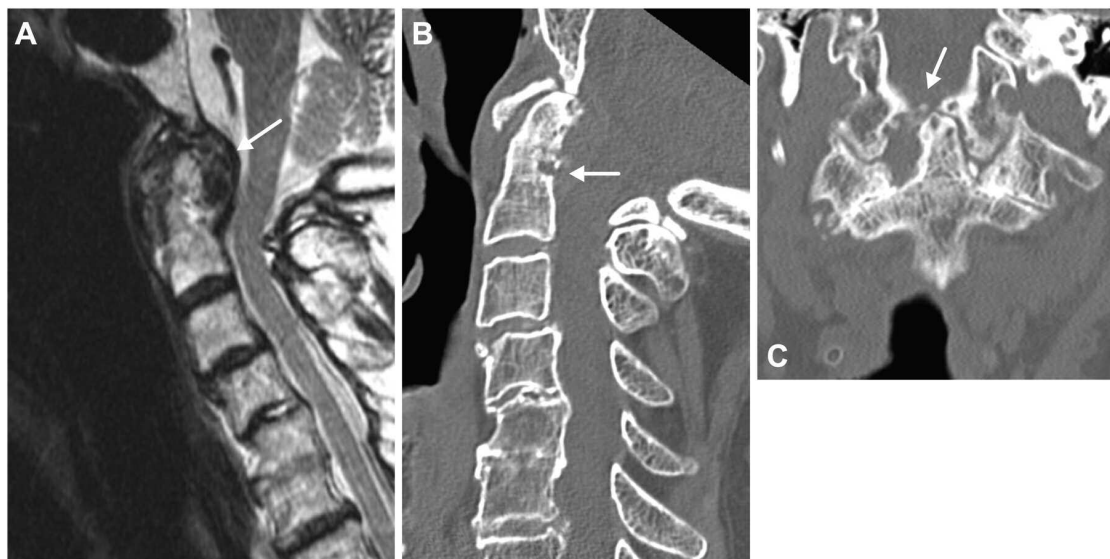


Figure 3. Atlanto-axial pannus in a 90-year-old female without RA presenting with neck pain and headaches. (A) Sagittal T2-weighted MRI image demonstrating a soft tissue mass (arrow) surrounding the odontoid process. (B) The sagittal CT image shows bony erosion of the odontoid with adjacent calcification (arrow). Marked degenerative changes are evident in the lower cervical spine. (C) The coronal CT image shows mineralization (arrow) around the odontoid process. Note the degenerative changes in the lateral atlanto-axial articulations.

Table 2. Characteristics of patients with atlanto-axial pannus without rheumatoid arthritis.

Characteristics	CPPD, n = 34	Other, n = 42	p
Age, yrs, median (IQR)	80 (73–86)	77 (71–84)	0.17
Sex			0.14
Female	22 (65)	20 (48)	
Male	12 (35)	22 (52)	
Race			0.68
White	29 (88)	36 (88)	
Hispanic	0 (0)	2 (5)	
Asian or Pacific Islander	1 (3)	1 (2)	
Black	3 (9)	2 (5)	
Pertinent clinical history			
Neck pain	24 (77)	23 (74)	0.77
Radicular pain or headache	12 (52)	16 (62)	0.51
Upper extremity motor or sensory deficit	12 (46)	13 (41)	0.67
Findings of myelopathy	12 (41)	12 (33)	0.51
Trauma	12 (35)	11 (28)	0.52
Prior cervical spine surgery	7 (21)	5 (15)	0.49
Cervical spine surgery after index MRI			
Any cervical spine surgery	12 (35)	10 (25)	0.33
Surgery of atlanto-axial region	5 (15)	8 (20)	0.62

Values are n (%) unless otherwise specified. Percentages were calculated excluding subjects with missing data. CPPD: calcium pyrophosphate dihydrate disease; IQR: interquartile range; MRI: magnetic resonance imaging.

region were not significantly different between patients with RA and those without (13.8 % vs 17.6%, $p = 0.64$).

DISCUSSION

Pannus in the atlanto-axial joint may develop through multiple mechanisms. In patients with RA, synovitis in the atlanto-axial joint can lead to inflammatory pannus formation akin to the destructive arthritis in peripheral joints²¹. Similarly, in crowned dens syndrome, CPPD-induced inflammation may cause pannus formation²². Other studies have suggested that atlanto-axial pannus may be the result of degenerative disease in the cervical spine leading to instability at the C1-C2 articulation and formation of reactive fibrous tissue^{12,23}. Studies combining MRI or CT imaging with histological analysis have revealed heterogeneity in the appearance of the atlanto-axial pannus tissue^{24,25}. While we have no histopathological data on the subjects in our cohort, the advanced age and history of prior cervical spine surgery in several non-RA patients supports the idea that degenerative changes⁶ contribute to atlanto-axial pannus formation in this group. Our finding of atlanto-axial calcification in 60.4% of the non-RA patients who had a cervical spine CT is consistent with a previous study that reported an age-related increase in atlanto-axial calcification, with imaging findings of calcification in 34% of individuals aged 60 years or older and in 49% of individuals aged 80 years or older²⁶. Such atlanto-axial calcium deposits were shown to represent CPPD in one study⁷. However, whether mineral deposition in the atlanto-axial joint is the primary driver of pannus formation or mostly a marker of degenerative disease in the cervical spine is unclear.

Studies have indicated that spine involvement is highly

Table 3. Characteristics of patients with atlanto-axial pannus undergoing cervical spine surgery.

Characteristics	Surgical, n = 28	Nonsurgical, n = 75	p	Surgery of AAR, n = 17	Other C-spine Surgery, n = 11	p
Age, yrs, median (IQR)	77.1 (69–84)	73.8 (63–83)	0.51	77.8 (69–79)	76.5 (68–85)	0.49
Pertinent clinical history						
Neck pain	16 (67)	52 (81)	0.15	11 (73)	5 (56)	0.41
Radicular pain or headache	6 (38)	30 (55)	0.23	4 (36)	2 (40)	1.00
Upper extremity motor or sensory deficit	14 (56)	22 (36)	0.09	7 (44)	7 (78)	0.21
Findings of myelopathy	13 (50)	23 (34)	0.16	7 (41)	6 (67)	0.41
Trauma	9 (32)	18 (24)	0.42	5 (29)	4 (36)	1.00
Prior cervical spine surgery	5 (18)	7 (10)	0.33	3 (18)	2 (18)	1.00

Values are n (%) unless otherwise specified. Percentages were calculated excluding subjects with missing data. IQR: interquartile range; AAR: atlanto-axial region.

prevalent in RA, with evidence of pannus found in up to 62.5% of cases on MRI²⁷. Despite having access to a large database, including data from 2 academic centers with large rheumatology outpatient clinics, we identified only 29 cases of RA-associated atlanto-axial pannus. Several factors may have contributed to this relatively low number: (1) RA patients with atlanto-axial disease may not have symptoms warranting cervical spine imaging²⁷; (2) providers may choose radiographs over MRI as the primary imaging modality in symptomatic RA patients with suspected atlanto-axial instability; (3) patients may have been missed by our search algorithm because of spelling errors or inaccessible MRI reports; (4) a small amount of atlanto-axial pannus may not be reported by the radiologist in a routine clinical setting; and (5) the prevalence of cervical spine involvement in RA may be declining. Most of the patients with RA in our study were diagnosed before the widespread introduction of biologic therapy. While the number of patients with RA was too low to detect any time trends, it is reasonable to assume that the current approach of treating RA early and aggressively is having a beneficial effect on the cervical spine⁶.

One of the objectives of this study was to determine how frequently atlanto-axial pannus is the presenting finding of RA in previously undiagnosed patients²⁸. Importantly, we found only 1 patient who was diagnosed with RA after the index MRI demonstrated the presence of atlanto-axial pannus. This patient was a 70-year-old woman with a history of polymyalgia rheumatica and bilateral total knee arthroplasties who was treated with hydroxychloroquine for arthralgias at the time of the MRI study. She was seronegative but had erosive changes on hand radiographs that her treating rheumatologist attributed to hand osteoarthritis. She was later diagnosed with RA by another rheumatologist. None of the other 76 non-RA patients had chart evidence for RA development over a median followup period of 3.6 years. A clinically important conclusion from this study is therefore that it is highly unlikely that a patient with incidental pannus in the atlanto-axial joint on MRI who does not already have a diagnosis of RA will subsequently be diagnosed with RA. A

1-time evaluation for current peripheral joint complaints should suffice to identify the rare patient with unrecognized RA. Extended followup to observe for the development of peripheral joint problems consistent with RA does not appear to be indicated. This is particularly true for older patients. Median age of the non-RA populations in our study was 79 (IQR 72–85) years. Most of these patients were over the age of 70 years, and only 2 patients without RA (2.6%) were less than 50 years old. One of these 2 had a history of JIA. The other had an atypical presentation of neck pain and stiffness without a clear rheumatologic diagnosis. This patient moved out of state and was lost to followup.

Roughly one-quarter of patients in our study population underwent cervical spine surgery after the index MRI, and fewer than two-thirds of these cases involved surgical intervention at the atlanto-axial level. This suggests that the identification of atlanto-axial pannus was not considered an indication for surgery in the majority of cases. Insufficient data were available to compare longterm outcomes in patients undergoing cervical spine surgery and patients managed conservatively.

A major strength of our study is the identification of cases of atlanto-axial pannus by free-text searching a large, multi-hospital EMR database. This helped to ensure that cases were identified regardless of provider specialty or clinical setting, thereby reducing the risk for selection bias. Further, MRI scans were reviewed by 2 blinded radiologists so that only confirmed cases of atlanto-axial pannus were included in the analysis. Limitations include the retrospective study design, which required us to depend on documentation from the electronic health record; patients with incidental atlanto-axial pannus were not evaluated according to a predefined standard protocol. Another limitation is the reliance on data from a single, albeit large, healthcare system, which may have resulted in incomplete data for patients who also received care outside the system. Additionally, as discussed above, cases of atlanto-axial pannus may have been missed in our database query because of spelling errors, word choices in the MRI report, or underreporting of minor imaging abnormalities.

In this study of 105 patients with atlanto-axial pannus found on cervical spine MRI, 27.6% had RA. Only a single individual, representing 1.3% of subjects without preexisting RA diagnosis, was diagnosed with RA after the index MRI, and this was a patient with longstanding peripheral joint complaints. This suggests that patients with incidental atlanto-axial pannus on cervical spine MRI are unlikely to have previously unrecognized RA. The non-RA patients in our study were significantly older than the patients with RA and frequently had evidence of tissue calcification, consistent with a role for degenerative disease or CPPD in the formation of atlanto-axial pannus in these patients. Although the term *pannus* is commonly associated with RA, the imaging finding of atlanto-axial pannus is clearly not pathognomonic for RA. More specific terminology and radiographic definitions of soft tissue masses about the atlanto-axial joint are desirable.

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