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RHEUMATOID ARTHRITIS (LW MORELAND, SECTION EDITOR)

# Radiological Findings of the Cervical Spine in Rheumatoid Arthritis: What a Rheumatologist Should Know

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## Abstract

**Purpose of Review** Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting mainly the peripheral skeleton in a symmetrical manner rather than the axial skeleton, but when it occurs it can affect the cervical spine (CS). Although CS involvement is a frequent radiographic finding in RA, the clinical features are scarce, but potentially life-threatening with severe neurological deficits or even death due to brain stem compression. The commonest site of inflammation of the CS is the articulation between $C_1$ and $C_2$ vertebrae, the atlanto-axial region. The radiological finding observed in this region is the atlanto-axial subluxation (AAS). For the evaluation of CS in RA the classical diagnostic technique used mostly is conventional radiography (CR). Since CR does not provide good information regarding synovial inflammation, other imaging modalities are used such as magnetic resonance imaging and computed tomography. However, CR is the most valuable tool for screening CS in RA patients. Thus, we reviewed the literature until December 2019 for studies regarding CS radiological manifestations using CR in RA patients.

**Recent Findings** We found that the frequency of radiological findings varies substantially, ranging between 0.7–95% in different studies. The commonest radiological feature was the AAS followed by subaxial subluxation.

**Summary** Because CS involvement can often be clinically asymptomatic, its assessment should not be forgotten by physicians and should be assessed using CR which is an easy to perform technique and gives important information as a screening tool.

**Keywords** Rheumatoid arthritis · Spine · Radiography · Diagnostic imaging · Complications · Neck pain · Joint instability · Cervical vertebra

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting mainly the peripheral skeleton in a symmetrical manner. It is a polyarticular disease affecting predominantly the small joints of the hands and wrists as well as the feet. RA does not have a predilection for the axial skeleton, but when it occurs, it can affect the cervical spine (CS) and the sternoclavicular joints [1, 2]. Clinical manifestations of CS involvement include as follows: neck pain and stiffness leading to a decreased range of motion (ROM). In some cases, the patients complain for a tingling sensation and numbness of the hands, the so-called marble sensation. The Sharp-Purser test may be used for the assessment of a possible anterior atlanto-axial subluxation (AAS). It has a predictive value of 85% and a specificity of 96%. Its sensitivity is 88% when the subluxation is > 4 mm [3]. Neurological examination may reveal brisk tendon reflexes, positive Babinski sign, and clones. Although CS involvement is a frequent radiographic finding in RA, the clinical features are scarce, but potentially life-threatening with severe neurological deficits or even death due to brainstem compression. Therefore, to avoid irreversible neurological complications, its diagnosis is an imperative and requires objective diagnostic modalities [4].

For the evaluation of the CS in RA, the classical diagnostic technique used mostly is conventional radiography (CR) [5]. On the other hand, CR does not provide good information regarding synovial inflammation or other soft-tissue structural changes. Thus, other imaging modalities are used, such as magnetic resonance imaging (MRI) and computed tomography (CT). MRI demonstrates active synovitis of the odontoid process, or pannus formation and erosions. Finally, a CT scan

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may visualize better the erosive changes of the disease [6]. However, CR is the most valuable tool for screening the CS in RA patients. It is an easy-to-perform technique and gives important information about CS involvement [5]. We reviewed the literature until December 2019 for studies regarding CS radiological manifestations in RA patients. In this review, we will discuss the value of CR as a screening tool for the evaluation of the CS and the radiological findings occurring in this setting.

## Cervical Spine Anatomy

The CS is composed of seven cervical vertebrae from $C_1$ to $C_7$ (cranial to caudal), from the base of the skull ($C_1$) down to the top of the shoulders ($C_7$). The anatomy differs among them. Superiorly, the topmost vertebra $C_1$ (atlas) and the $C_2$ (axis) tend to be smaller and more mobile, facilitating in this way the head movements such as flexion, extension, lateral flexion, and rotation. On the other hand, the lower CS vertebrae are larger in order to handle greater loads from the neck and head (Fig. 1). Atlas is the only vertebra without a vertebral body. It is an atypical, ring-shaped vertebra articulating to the occipital bone in order to support the base of the skull forming the atlanto-occipital joint. The second cervical vertebra ($C_2$) has a large bony protrusion, the odontoid process or dens, that extends upward from its vertebral body and fits into the atlas forming the atlanto-axial joint. Unlike other vertebral joints, this joint does not have an intervertebral disc. The dens is held in place by a thick strong ligament, i.e., the transverse ligament, and by the alar and apical ligaments. The rest of the CS vertebrae bellow $C_2$ are known as typical vertebrae because they share the same basic characteristics with the other vertebrae of the spine. They separate between them by an intervertebral disc [7, 8].

## Radiological Evaluation of CS in RA Patients

CR of the CS gives important information for cervical instability if used correctly as a screening tool in patients with RA. The radiological evaluation of the CS comprises radiographs

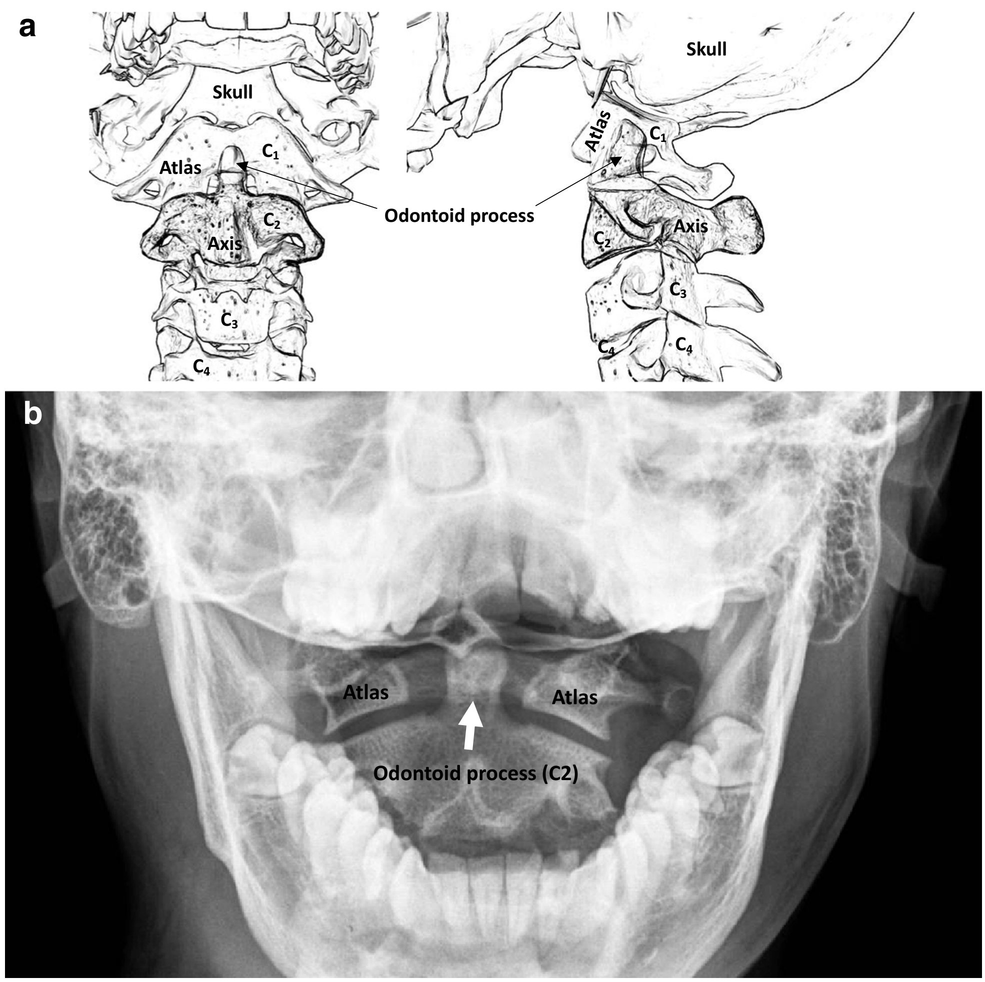


**Fig. 1** **a** The atlanto-occipital and the atlanto-axial joints in the anterior and lateral views respectively. The axis ($C_2$) in bold order denotes the odontoid process. The atlas ($C_1$) is the first cervical vertebra. **b** The odontoid process of $C_2$ through mouth view projection

of the CS in antero-posterior (AP), upright, lateral, flexion, and extension views. In frontal plane, an open-mouth x-ray may be useful for a better visualization of the odontoid process (Fig. 1). With this radiological approach, bone alignment, bone quality, deformities, and CS instability can easily be assessed. If any CS abnormality is suspected or confirmed with CR, then, other imaging modalities such as MRI or CT scan must be performed. MRI is the most sensitive imaging modality for the evaluation of CS abnormalities in RA patients. Active synovitis of the odontoid process, pannus formation, ligament laxity, and erosions can all be assessed by using MRI. Finally, CT scan of the CS with multiple projection reconstruction (MPR) is superior in demonstrating any erosive changes [5, 6].

## Radiological Findings of CS in RA Patients Using CR

The commonest site of inflammation of the CS is the articulation between $C_1$ and $C_2$ vertebrae, the atlanto-axial region. The radiological finding observed in this region is the AAS. AAS is the instability of the atlanto-axial joint due to weakening of the structures or rupture of ligaments as well as subchondral bone erosions [9–11]. Subaxial subluxation (SAS) of the CS is defined as the segment bellow the $C_2$ vertebra that is from $C_3$ to $C_7$. Other CS abnormalities comprise the following: upper disc space narrowing, vertebral plate erosions and sclerosis, and apophyseal joint erosions and sclerosis. CS abnormalities as described above are frequent radiographic findings in RA patients, but the clinical features are scarce and minimal but potentially life-threatening. One of the most common and with underlying risk radiographic finding in CS is AAS [12–14].

## Radiological Findings of AAS

The AAS is characterized by excessive movement at the junction between the $C_1$ and the $C_2$ vertebrae as a result of bony erosions and ligament abnormality. The atlanto-axial joint can be subluxed in multiple directions leading to cervical cord compression, and cause myelopathy [4, 9, 12]. The atlas can move anteriorly, posteriorly (Fig. 2), laterally, vertically, or rotationally related to the odontoid process of the axis (Fig. 6). More specifically, there is an articulation between the transverse ligament of the atlas and the posterior aspect of the odontoid process. This thick and strong articulation acts as a sling in maintaining constant the odontoid process against the posterior surface of the atlas and to prevent forward movement of $C_1$ on $C_2$ vertebrae. Persistent inflammation of this articulation may produce dens erosions; damage of the transverse, alar, and apical ligaments; and laxity leading to joint instability [5, 6]. The distance between the anterior aspect of the odontoid process and the posterior surface of the anterior arch of the atlas usually measures $\leq 3$ mm (Fig. 3a). If this distance increases and exceeds more than 8 mm, the chance of CS cord compression is high (Fig. 3b). However, the posterior atlanto-dental distance has been found to be a better predictor for cord compression. Indeed, the distance from the posterior border of the dens to the anterior aspect of the posterior arch of the $C_1$ vertebra, represents the maximum amount of space for the CS cord. In detail, in CS, the cord occupies 10 mm of the canal diameter, and 1 mm requires for the dura and 1 mm for the CS fluid anterior to the cord and 1 mm posteriorly. Thus, the total space is 14 mm. If the available space becomes < 14 mm, then the CS cord becomes compressed. Thus, in AAS, if the anterior atlanto-dental distance increases more than 3 mm and the posterior atlanto-dental distance decreases less than 14 mm, then the CS cord is prone to compression [15].

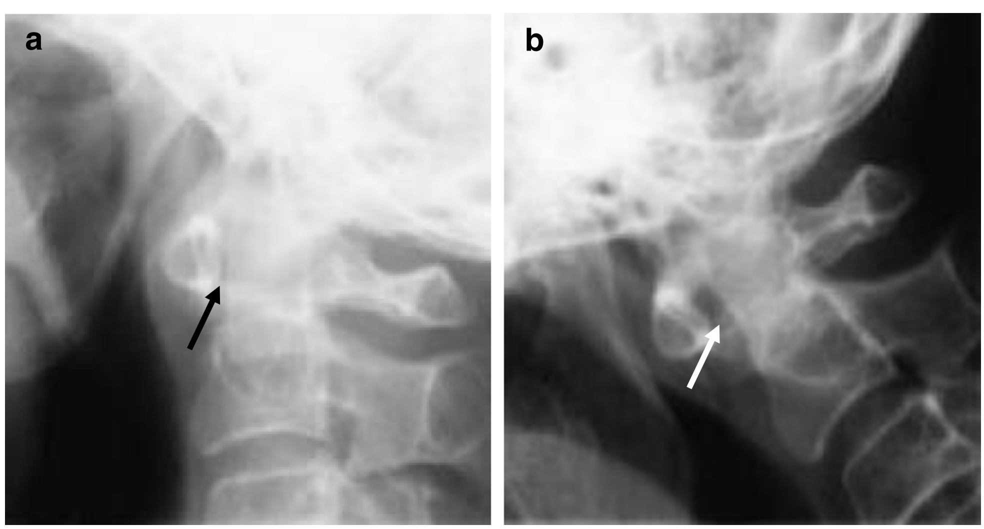


**Fig. 2** Atlanto-axial subluxation (AAS) in neutral position of the neck (**a**) and anterior flexion (**b**). Note that in neutral position, the space between the posterior surface of the anterior arch of the atlas and the anterior aspect of the odontoid process is not well visualized (2 mm) and may be missed (black arrow). Thus, an x-ray of the neck must be done in flexion in order to reveal the real space between the two anatomical structures (6 mm—white arrow)

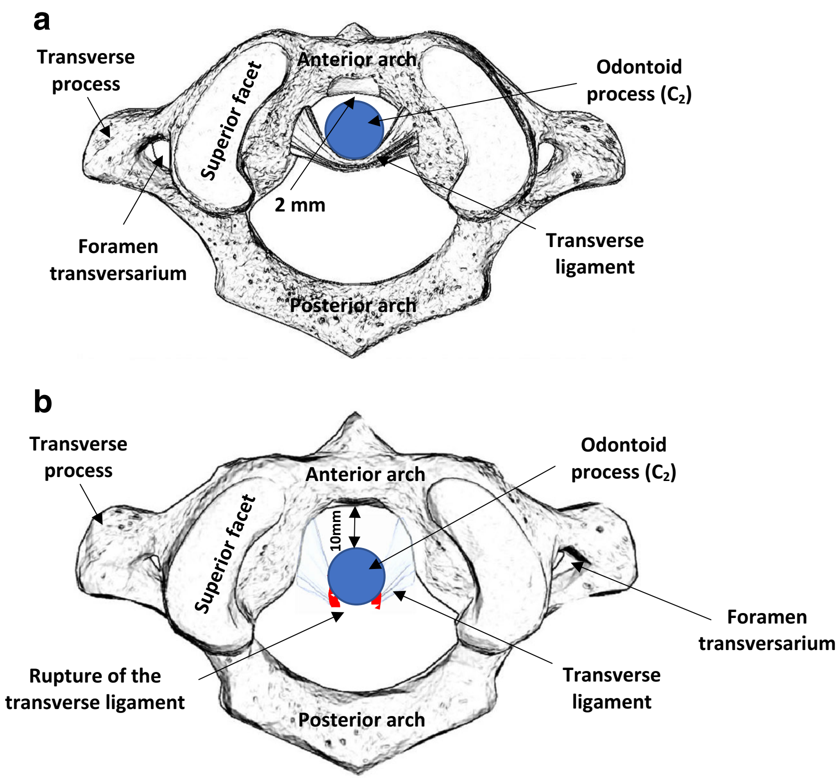


**Fig. 3** **a** Schematic representation of the atlanto-axial joint in a healthy individual. Anatomy of the first cervical vertebra (atlas/$C_1$). Note also the odontoid process of the $C_2$ vertebra (axis) as well as the synovial membrane that lines the dens anteriorly and posteriorly. The distance between the anterior aspect of the odontoid process and the posterior surface of the anterior arch of the atlas (facet for dens) should measure ≤ 3 mm. **b** Schematic representation of the atlanto-axial subluxation in a patient with RA. After rupture of the transverse ligament, there is an anterior translocation of the atlas ring and posterior movement of the odontoid process. Note that the distance between the anterior aspect of the odontoid process and the posterior surface of the anterior arch of the atlas is approximately 10 mm. In this situation, the chance of CS cord compression is very high and life-threatening

## Radiological Findings of the Lateral AAS

Lateral AAS of the CS in RA is rare and occurs sporadically resulting in a rotational deformity. The open-mouth view is useful for its evaluation. Lateral AAS can be suspected when asymmetry or lateral displacement of the atlas on the axis by > 2 mm or an asymmetrical collapse of the lateral mass takes place, when an open-mouth radiography view is used [6].

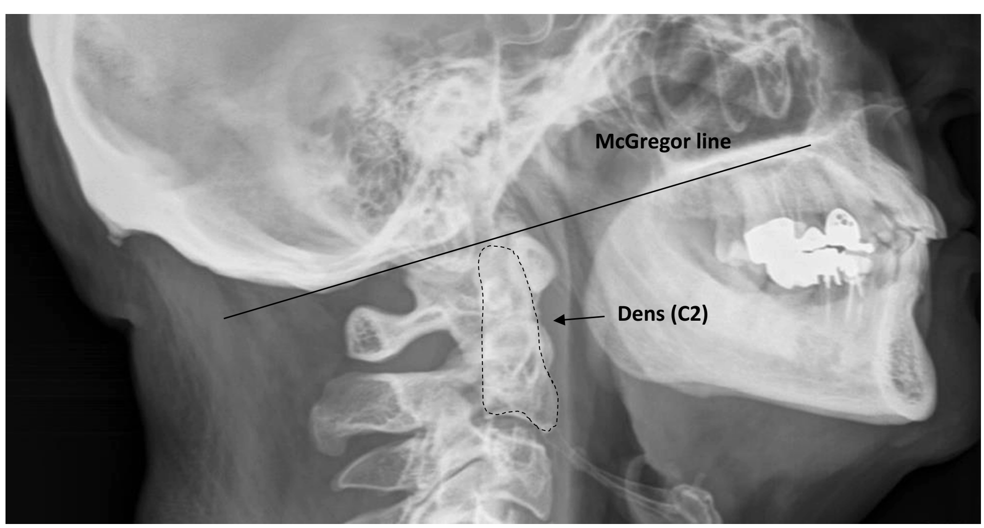


**Fig. 4** McGregor's line is a hypothetical line drawn between the hard palate and the most caudal point of the occipital curve. When the odontoid tip is > 4.5 mm above McGregor's line, then basilar invagination is considered

## Radiological Findings of the Vertical AAS

Vertical AAS, also known as basilar impression on cranial setting, is a superior migration of the odontoid process resulting in brainstem compression by the dens and/or the pannus itself. It may cause stroke, obstructive hydrocephalus, heart arrest, and sudden death [16]. Vertical AAS is present if the tip of the dental peg lays > 4.5 mm above the McGregor line [17]. This is a hypothetical line drawn between the hard palate and the most caudal point of the occipital curve (Fig. 4).

## SAS in CS in RA Patients

SAS affects the $C_3$ to $C_7$ vertebrae. It is the second more common form of CS instability in RA patients. It occurs when inflammation involves the apophyseal joints, the intervertebral disc, and the interspinous ligaments. Anterior SAS is much more common than posterior SAS. It can be an isolated finding involving one or more levels, but when SAS involves multiple levels, it can lead to a "staircase" deformity (Figs. 5 and 6). Its diagnosis should be considered on > 3.5-mm horizontal displacement of one vertebra in relation to an adjacent one, when it is measured on a lateral CR view. The clinical outcome of SAS is similar or even worse to that of AAS with the involvement of late neurological complications. It may also occur simultaneously with AAS. In this case, the CS stability may deteriorate even more with severe neurological consequences [11, 18].

**Anterior**: occurring in the anterior median atlanto-axial joint, located between the anterior arch of $C_1$ and the dens of the axis.

**Posterior**: occurring in the posterior median atlanto-axial joint, located between the posterior arch of $C_1$ and the dens of the axis.

**Lateral**: asymmetrical or unilateral changes of the atlanto-axial joint leading to impairment in rotation.

**Vertical**: the superior migration of the odontoid process into the foramen magnum.

**Fig. 6** Possible types of the atlas dislocation in AAS

Despite the fact that a significant number of RA patients present with radiographically detectable CS abnormalities, only a small number will develop CS myelopathy or other neurological complications. In Table 1, we present the CS radiological abnormalities in RA patients. Below, we present the studies investigating the CS involvement in RA patients.

## Studies Investigating the CS Involvement in RA Patients

The diagnosis of CS involvement among RA patients is extremely important because it is associated with high morbidity

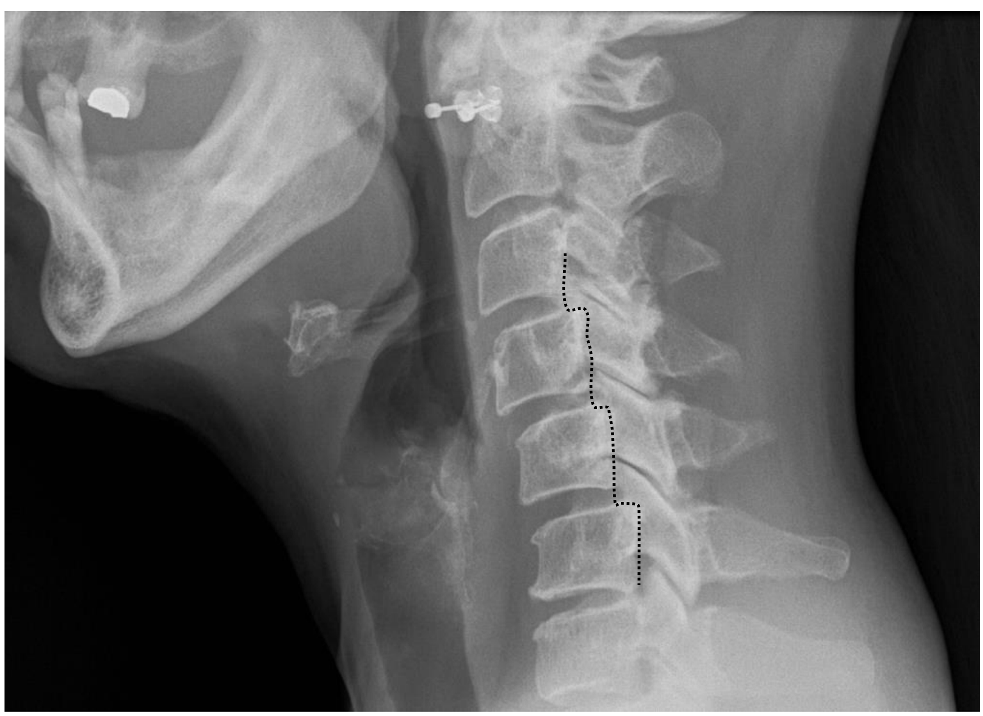

**Fig. 5** Subaxial subluxation at the $C_3$–$C_4$, $C_4$–$C_5$, and $C_5$–$C_6$ levels. Note the "staircase" deformity (black dotted line)

**Table 1** Radiological findings/involvement of CS in RA patients

| Author | Year | Country | Nr. of patients | Cervical spine involvement (%) | Mean age | Disease duration (years) |
|---|---|---|---|---|---|---|
| Sharp [19] | 1958 | UK | 44 | 40% | | 7.5 |
| Bland [20] | 1963 | USA | 100 | 86% (25% severe involvement) | 56 | 14.4 |
| Serre [21] | 1964 | France | 60 | 38% | | |
| Conlon [22] | 1966 | New Zealand | 333 | 50% (AAS 22%) | 52.7 | 5–10 |
| Park [23] | 1969 | USA | 100 | 37% AAS, 24% $C_2$–$C_4$ subluxation | | 10 |
| Meikle [24] | 1971 | Scotland | 118 | 37.3% AAS, 26.3% SAS | 57.6 | 12.9 |
| Isdale [25] | 1971 | New Zealand | 171 | 80.7% (AAS 46%)—follow-up study of Conlon et al. | | 11–16 |
| Stevens [26] | 1971 | UK | 100 | 36% AAS | 54.2 | 11.3 |
| Smith [27] | 1971 | UK | 962 | 15.6% (2% spinal cord/brainstem involvement) | 51.3 | 7.4 |
| Ornila [28] | 1972 | UK | 77 | 23% | 52 | 10 |
| Henderson [29] | 1973 | UK | 476 | 3.7% AAS | 59 | 22.2 |
| Shaw [30] | 1976 | UK | 100 | AAS is a common complication | 54.2 | |
| Chevrot [31] | 1978 | France | 577 | 28% | | |
| Cabot [32] | 1978 | USA | 53 | 52% (36% significant $C_{1-2}$ anterior subluxation) | | 4–35 |
| Rasker [33] | 1978 | Netherlands | 62 | 42% AAS, 32% vAAS | 61.1 | 14.6 |
| Winfield [34] | 1981 | UK | 100 | 33% | 54.8 | 7.7 |
| Pellici [35] | 1981 | USA | 106 | 81% | 62.6 | 30.1 |
| Halla [36] | 1982 | USA | 126 | 27% anterior AAS, 25% vertical AAS, 7% SAS | 57.6 | 11.1 |
| Winfield [37] | 1983 | UK | 100 | 54% (5% AAS, 24% SAS, 5% both) | 57.1 | 10 |
| Haaland [38] | 1984 | Norway | 104 | 45% | | 15.3 |
| Redlund-Hohnell [39] | 1985 | Sweden | 450 | 18% | 63.5 | |
| Morizono [40] | 1987 | Japan | 100 | 49% AAS, 26% upward migration of the odontoid | 57.1 | 12.8 |
| Halla [41] | 1990 | USA | 310 | 10.9% | 68.8 | 10.2 |
| Collins [42] | 1991 | USA | 113 | 61% | 55 | 15 |
| Veerapen [43] | 1993 | Malaysia | 140 | 17.1% (12.4% AAS) | 46.5 | 10.1 |
| Kaupi [44] | 1994 | Finland | 98 | 54% (33% aAAS, 21% SAS) | | 15.7 |
| Montemerani [45] | 1994 | Italy | 183 | 30% AAS | 33.4 | 12.3 |
| Stiskal [46] | 1995 | Austria | 136 | 43.3% | 57 | 13 |
| Aggarwal [47] | 1996 | India | 100 | 65% (24% AAS) | | > 5 |
| Paimela [48] | 1997 | Finland | 67 | 30% | | 6.5 |
| Fujiwara [49] | 1998 | Japan | 173 | 43% | 55.6 | 12.5 |
| Yoshida [50] | 1999 | Japan | 161 | 42.4% (22.5 AAS, 10.1 SAS) | 59.5 | 16.5 |
| Neva [51] | 2000 | Finland | 176 | 8.3% (3.4% aAAS, 2.8% SAS) | 48.5 | 2.5 |
| Riise [52] | 2001 | Norway | 241 | 8.9% (5% aAAS) | 61.9 | 5.4 |
| Laiho [53] | 2001 | Finland | 25 | 87% (39% aAAS) | | 17.3 |
| Carmona [54] | 2003 | Spain | 788 | 12.1% AAS | 61 | 10 |
| Mitsuka [55] | 2004 | Japan | 174 | 60% | 60.9 | 19.1 |
| Pisitkun [56] | 2004 | Thailand | 134 | 68.7% (26.9% aAAS, 14.9% pAAS, 17.2% lAAS, 16.4% vAAS) | 48.9 | 5 |
| Naranjo [57] | 2004 | Spain | 736 | 12% | 61.4 | 9 |
| Schwarz-Eywill [58] | 2005 | Germany | 214 | 69.5% | | 17.3 |
| Zikou [59] | 2005 | Greece | 165 | 88% (20.6% AAS, 43.6% SAS) | 59.6 | 12.3 |
| Vesela [60] | 2005 | Czech Rep. | 400 | 45.8% | | 18.5 |
| Raczkiewicz [61] | 2006 | Poland | 100 | 50% (15% AAS, 18% SAS, 9% basilar invagination) | 61.4 | 12.5 |
| Yan [62] | 2008 | China | 71 | 95% | 46.2 | 18.2 |
| Younes [10] | 2009 | Tunisia | 40 | 72.5% (45% AAS–25% aAAS, 15% lAAS; 10% SAS) | | 10 |
| Imagama [63] | 2010 | Japan | 100 | 45% AAS | 61 | 13 |
| Ahn [64] | 2010 | Korea | 1120 | 28.6% (among those 89.7% AAS, 15% SAS) | - | > 3 |
| Yurube [65] | 2011 | Japan | 267 | 47.5% vs 70.4% (entry study vs end of the study) | - | - |
| Yurube [66] | 2012 | Japan | 140 | 43.6% (12.9% with severe cervical instabilities) | 68.3 | 18.5 |
| Eser [67] | 2012 | Japan | 150 | 0.7% | 53.2 | 12.3 |
| Blom [9] | 2013 | Netherlands | 134 | 16% | 60.6 | 9.5 |
| Kaito [68] | 2013 | Japan | 91 | 48.3% (31.8% AAS) | | |
| Takahashi [69] | 2014 | Japan | 220 | 42% | | |
| Nazarinia M [70] | 2014 | Iran | 100 | 10% AAS, 6% SAS | | |
| Ibrahim [71] | 2015 | Japan | 201 | 42.3% | 62.3 | 12.9 |
| Macovei [72] | 2016 | Romania | 107 | 33% | 65 | 17 |
| Kaito [73] | 2017 | Japan | 151 | 28% AAS, 4% SAS | 50.6 | 8.5 |
| Morita [74] | 2019 | Japan | 296 (1999) | 49.3% AAS, 24.3 SAS | 57.1 | 12.8 |
| | | | 1333 (2015) | 25.3% AAS, 19.3 SAS | 65.1 | 13.6 |
| Chung [75] | 2019 | Korea | 242 | 48.3% AAS (2.3% basilar invagination) | 56.6 | |
| Sandstrom [76] | 2019 | Finland | 85 | 4.7% (2.4% AAS, 1.2% SAS) | | |

*CS*, cervical spine; *RA*, rheumatoid arthritis; *AAS*, atlanto-axial subluxation; *aAAS*, anterior AAS; *pAAS*, posterior AAS, *lAA*, lateral AAS; *vAAS*, vertical AAS; *SAS*, subaxial subluxation and mortality [52, 77]. Because CS involvement can often be clinically asymptomatic, its assessment should not be forgotten by physicians. However, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations, as to when to evaluate the CS in RA, are missing [78]. Most of the studies are describing patients with CS involvement as a late manifestation during the disease course and in some cases as the presenting symptom. In Table 1, we present the studies investigating the CS in RA [9, 10, 19–76]. The majority of them are cross-sectional or retrospective and only few in a prospective design. RA disease duration was high ranged between 2.5 and 30.1 years (approx. 12.3 years on average). The incidence of CS involvement ranged between 0.7 in Japan [67] and 95% in China [62], and the CS abnormalities were assessed using CR. The commonest radiological features were AAS followed by SAS. Symptoms ranged from asymptomatic to localized head and neck pain with stiffness and few presented neurological manifestations. The majority of RA patients were seropositive while a few were seronegative. The diagnosis of CS involvement in RA requires a detailed questionnaire for symptoms, minute musculoskeletal and neurological examination, and radiological assessment with CR as a screening test. Usually, there is a discrepancy between the clinical symptoms of CS involvement and the radiological abnormalities occurring in this setting. Only one study of RA patients with CS disease showed correlation between clinical symptoms, neurological manifestations, and radiological damage [79]. In the absence of clinical symptoms, if AAS or SAS or atlanto-axial impaction is present in the radiological assessment, then attention is required for surgical consultation [15, 80].

## Discussion

The frequency of radiological findings of the CS in RA patients varies substantially, with a referred range of 0.7–95% in different studies [9, 10, 19–76]. This wide range of variation is related to the study design of the published reports. The majority of the published studies are cross-sectional and retrospective with only a few to be designed for early RA [81]. Radiological findings of the CS are considered a late manifestation of RA with multiple factors to be implicated. Long-disease duration, suboptimal treatment or patients with no treatment, seropositivity, high acute phase reactants, polyarticular disease, and the severity of structural joint damage of the peripheral joints are some of them [3, 4, 77, 82].

The commonest radiological abnormalities of the CS are AAS, followed by SAS and vertebral plate erosions with sclerosis as well as apophyseal joint disease. The commonest clinical symptoms in this setting are neck pain and stiffness, and the clinical examination reveals decreased ROM of the CS. Neurological involvement may be present in some patients [4, 6, 77]. It is reported that symptoms and signs differ widely across patients but show no correlation with the severity of radiological findings of the CS [4, 6, 77]. Patients with radiological abnormalities of the CS may be asymptomatic. In this context, it is difficult to determine the optimal time of ordering CR for the evaluation of the CS. This may be of particular importance as AAS can develop rapidly in some cases.

Although the frequency of radiological CS involvement is high, the severity of the disease is rather mild and only a small number of them present severe radiological findings. Thus, CR of the CS should be obtained regularly to seek for any CS radiological abnormalities, even in patients without evident symptomatology. However, prospective studies investigating the incidence of CS involvement in RA are missing and this must be done in a community-based design. Regarding the radiological assessment of the CS, the AAS becomes apparent when the radiographs are obtained in the lateral flexed position of the CS. If other views are used, this abnormality will be missed. Other imaging modalities that can be used to evaluate the CS involvement in RA are the MRI and CT. The most sensitive is MRI which shows the pannus formation, dens erosions, ligament laxity, or damage. CT scan with MPR is a better technique to evaluate the bone anatomy and erosive disease [5, 6, 77].

Treatment of RA has changed in the last two decades. The introduction of biological (b) disease-modifying anti-rheumatic drugs (DMARDs) has revolutionized RA management [83, 84]. In addition, the ACR and EULAR recommendations with the treat-to-target (T2T) approach using conventional synthetic (cs) or targeting synthetic (ts) DMARDs, along with bDMARDs, have changed the course and outcomes of RA disease progress [85]. Indeed, patients receiving the combination csDMARD therapy rarely developed CS disease, as compared with those receiving monotherapy [86]. In addition, the use of bDMARDs also prevented new CS abnormalities in RA [87] while other reports showed reduction of CS pannus formation and amelioration of clinical symptoms with the use of bDMARDs [68]. What is missing in this setting? It is a prospective study investigating the incidence of CS in RA patients and the role of T2T approach of preventing the CS disease.

## Conclusions

Radiological abnormalities of the CS in RA are not uncommon. The clinical symptoms and signs may differ widely across patients and show no correlation with the severity of radiological damage. In RA patients without significant clinical symptoms, screening of the CS with CR is recommended. The most common radiological abnormality is AAS followed by SAS. Knowledge of CS anatomy and its relationship with plain radiographs is essential to diagnose any CS instability.

**Authors' Contributions** All authors have participated equally for the production and approval of the final manuscript.

**Data Availability** Upon request

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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