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Imaging in Rheumatic Diseases

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Keywords

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Introduction

Imaging in the realm of rheumatic and musculoskeletal diseases (RMD) has evolved significantly over the past decade. It has become extremely important in the timely diagnosis, management/treatment and follow-up of RMD. Years ago the joint-imaging in a patient with rheumatoid arthritis (RA - more aptly called rheumatoid disease because it is not just a disease of the joints but rather a systemic inflammatory immune mediated rheumatic disease that can have several extra-articular manifestations/complications including interstitial lung disease, pleuritis/pericarditis, mononeuritis multiplex, secondary Sjogren's syndrome etc.) was almost limited to plain radiographs. The 'classic triad' of juxta articular erosions, symmetrical joint space narrowing and periarticular osteopenia was pretty much all that we could see at the time of diagnosis and follow-up of these patients. With time, magnetic resonance imaging of the joint started revealing many subtler findings including synovitis, tenosynovitis, synovial effusion etc. The advent of musculoskeletal ultrasonography has picked up pretty quickly over the past decade and now with a point-of-care ultrasound (POCUS), during the clinic visit itself, multiple revelations can come especially when Doppler signal is present in the synovium or tenosynovium suggesting active synovitis and tenosynovitis respectively. Similarly with psoriatic arthritis and other forms of spondyloarthritis, the clinical finding of a sausage digit (or 'carrot digit' respecting the vegetarians, the presence of tenosynovitis, synovitis, synovial effusion, and much more using POCUS help see the whole situation with a 'hawk's eye' rather than with the limited human eye. Revelation of tenosynovitis of the extensor carpi ulnaris tendon at the wrist as one of the classic findings of early/very early rheumatoid disease is very humbling. This has decreased the hiatus/lag from the symptom-onset to diagnosis and effective treatment is started. Time is of the essence when it comes to systemic inflammatory immune mediated rheumatic diseases. There is a definite window of opportunity from the onset of inflammatory joint symptoms to when the irreversible joint damage starts occurring. This critical window of opportunity is typically close to only 6 months FIG. With this introduction, we will be learning about the importance of various forms of imaging in various systemic inflammatory as well as localized noninflammatory RMD.

Plain radiography still has its own role especially in rural communities where advanced forms of imaging might not be available readily. Of course the tenet of ALARA "as low as reasonably achievable avoiding exposure to radiation that does not have a direct benefit to the operator, even if the dose is small" has to be followed under all circumstances. In a pregnant patients, understanding that diseases like systemic lupus erythematosus (SLE) and RA are much more common, especially in younger women of childbearing age, radiation exposure should be avoided especially during the first trimester when organogenesis is occurring in the fetus.

Rheumatoid Arthritis

As mentioned in the introduction, the radiographic triad of juxta articular osteopenia symmetrical joint space narrowing and subchondral/periarticular erosions is considered to be classic of RA. These radiographic findings have not been incorporated into the American College of Rheumatology (ACR)/European Alliance of Association for Rheumatology (EULAR) classification criteria for rheumatoid arthritis [1]. For follow-up imaging of RA, plain

radiography can still have its own place but it is pretty quickly getting replaced by POCUS, which can show synovitis (hypoechoic density within the joint space - especially active if there is Doppler signal in it), synovial effusion (anechoic compressible and displaceable material within the joint space without a Doppler signal), erosions (intra-articular discontinuity of bone surface that is visible in two perpendicular planes) etc. [2]. Interstitial lung disease can be seen in RA, especially the seropositive version can also be picked up on plain radiography of the chest. However, the sensitivity and specificity is quite low compared to high resolution computerized tomography (HRCT) of the chest.

In advanced, destructive, strongly seropositive, inadequately treated RA; involvement/erosion of the atlantoaxial ligaments can lead to a potentially serious complication called atlantoaxial dislocation. It can lead to quadriparesis pretty quickly and can even be fatal if the subluxed odontoid process of the second cervical vertebra pierces into the brainstem. Plain radiography can be helpful but computerized tomography (CT) scanning and magnetic resonance imaging (MRI) have a much higher yield for this potentially challenging involvement of the upper cervical spine in RA - virtually the only part of the spine that is involved in this condition (lower cervical, thoracic and lumbosacral regions of the spine are spared by RA!).

Psoriatic Arthritis (PsA)

There are 5 major clinical subgroups of PsA depending upon the pattern of joint/arthritic involvement [3]: symmetrical peripheral polyarthritis (>5 joints) that can mimic RA, asymmetric to peripheral oligoarthritis (2-4 joints), axial disease simulating axial spondyloarthritis (Ax SpA) with sacroiliitis, syndesmophytes (asymmetric) etc., involvement of the distal interphalangeal joints only, and a rather challenging entity of *arthritis mutilans* with multiple peripheral joints getting destroyed rather quickly by relentlessly progressive PsA.

The classic findings of 'pencil in cup' and 'opera-glass/telescoping' occur when PsA has been allowed to progress without a timely diagnosis and management. Hence the importance of POCUS, yet again, in the early diagnosis and timely management of PsA. In today's day and age, the fifth subset of *arthritis mutilans* should not be seen in the ideal world. These crippling joint deformities are technically irreversible with medical management.

Axial spondyloarthritis (Ax SpA)

In advanced stages, the classic radiographic 'bamboo spine' appearance of the spine (Figure 1) is a late, and hence, not a 'kind' finding for the patient. By that time, irreversible damage to the spine has occurred, which could have been prevented by early detection and management. Sacroiliitis 'wing' is one of the two wings of the ASAS criteria for Ax SpA [4]**,** Plain radiographs of the sacroiliac joints (SIJ) or anteroposterior radiographs of the pelvis to include SIJ, the hip joints, and lower part of the lumbar spine still have a role in this condition. However, the interobserver and intraobserver variation/variability when it comes to picking up 'early' sacroiliitis, and more so 'grading' sacroiliitis has always been challenging for both rheumatologists & radiologists. On the other hand short-tau-inversion-recovery (STIR) MRI of the SIJ and the lumbosacral spine [5] can provide a wealth of information about early changes of Ax SpA including bone marrow edema/ osteitis and erosions (Figure 2).

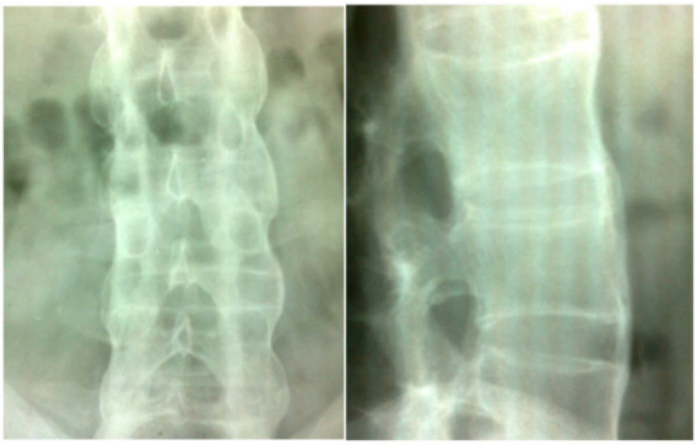


Figure 1: 'Bamboo spine' in AS – please note the extensive bridging syndesmophytes.

Attribution

Manoj E, Ragunathan M. Disease flare of ankylosing spondylitis presenting as reactive arthritis with seropositivity: a case report. J Med Case Rep. 2012 Feb 14;6:60. doi: 10.1186/1752-1947-6-60. PMID: 22333429; PMCID: PMC3295684.

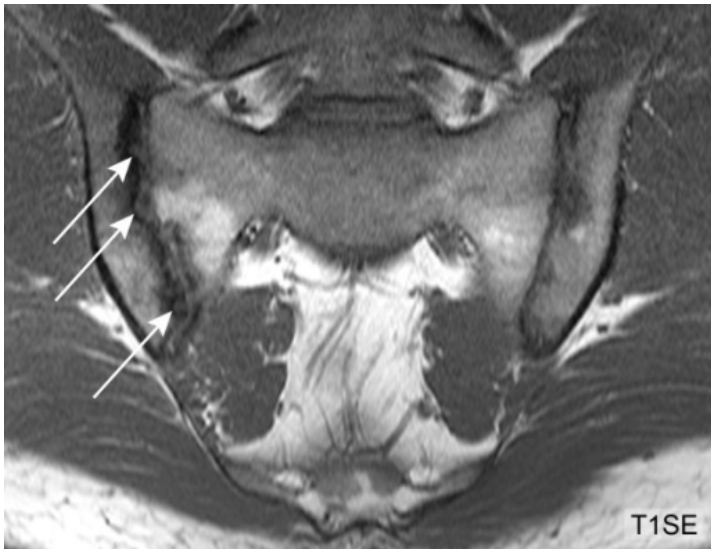


Figure 2: T1-weighted spin echo (T1SE) sequence. Erosion in the right ilium extending across the entire joint (arrows).

Attribution

Weber U, Pedersen SJ, Østergaard M, Rufibach K, Lambert RG, Maksymowych WP. Can erosions on MRI of the sacroiliac joints be reliably detected in patients with ankylosing spondylitis? - A cross-sectional study. Arthritis Res Ther. 2012 May 24;14(3):R124.

doi: 10.1186/ar3854. PMID: 22626458; PMCID: PMC3446505.

However, there are still challenges in the universal acceptance and embracement of grading of sacroiliitis and spinal involvement among radiologists and rheumatologists. Fortunately, the gap is getting narrowed with time! Another challenge is the entity of 'non radiographic' Ax SpA in which the classic radiographic findings radiographic Ax SpA (also referred to as ankylosing spondylitis) are not present. It has been considered to be an independent form of the disease by itself which can still lead to a lot of morbidity or on the spectrum Ax SpA which might become 'radiographically evident' down the road. The treatment of non-radiographic Ax SpA also requires use of nonsteroidal anti-inflammatory agents, conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) which are not typically very effective and certain biologics including tumor necrosis factor alpha inhibitors, Interleukin 17 inhibitors and targeted synthetic DMARDs like Janus kinase inhibitors.

One of the complications of Ax SpA is loss of bone mineral density/frank osteoporosis that can result in spinal fractures. Although there is 'extra' bone formation in this group of diseases, this is abnormal/brittle bone and can break very easily even with a minor injury like a jolt. Plain radiographs might not be very efficient in picking up a subtle spinal fracture compared to CT scan or MRI. Similarly, another potential complication of advanced AS is the *cauda equina* syndrome that typically presents with saddle anesthesia and progressive neurological deficits including bladder/bowel incontinence and requires urgent imaging especially MRI towards timely diagnosis and management for a favorable outcome.

Gout

It is a widely prevalent form of inflammatory arthritis despite being a completely preventable and totally reversible condition. It is one of the most painful, if not the most painful situations that reflects mankind [6].

Lifestyle medicine remains the key to prevent and even reverse this 'scourge of mankind'. The classic plain radiographic findings of punched-out erosions with overhanging edges with preservation of joint space especially in the first metatarsophalangeal (MTP) joint of the foot have been considered classic for gout. However, with POCUS, early detection of synovitis synovial effusion and some very special findings including double contour sign, blizzard sign and 'wet sugar clumps' sign (intra/periarticular tophi) can help substantiate the diagnosis of gout without the necessity of performing challenging arthrocentesis like the first MTP joint. Double contour sign (Figures 3A, 4) has now been incorporated into the ACR classification criteria for gout [7].

Attribution

Zufferey P, Valcov R, Fabreguet I, Dumusc A, Omoumi P, So A. A prospective evaluation of ultrasound as a diagnostic tool in acute microcrystalline arthritis. Arthritis Res Ther. 2015 Jul 22;17(1):188. doi: 10.1186/s13075-015-0701-7. Erratum in: Arthritis Res Ther. 2015 Sep 16;17:255. doi: 10.1186/s13075-015-0746-7. Pascal, Zufferey [corrected to Zufferey, Pascal]. PMID: 26198435; PMCID: PMC4511437.

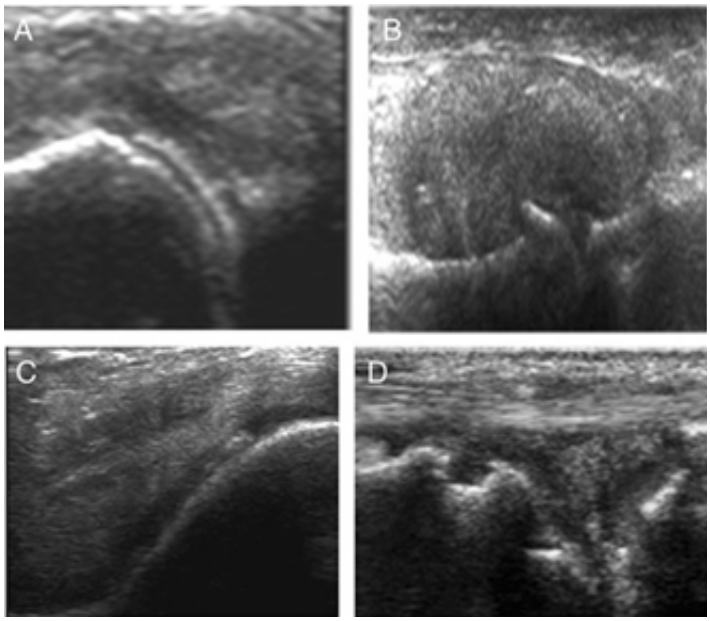


Figure 3: A. double contour sign in gout; B. A gouty tophus sonographically. Intra-cartilage linear (C) and meniscal (D) hyperechoic deposit of CPPD.

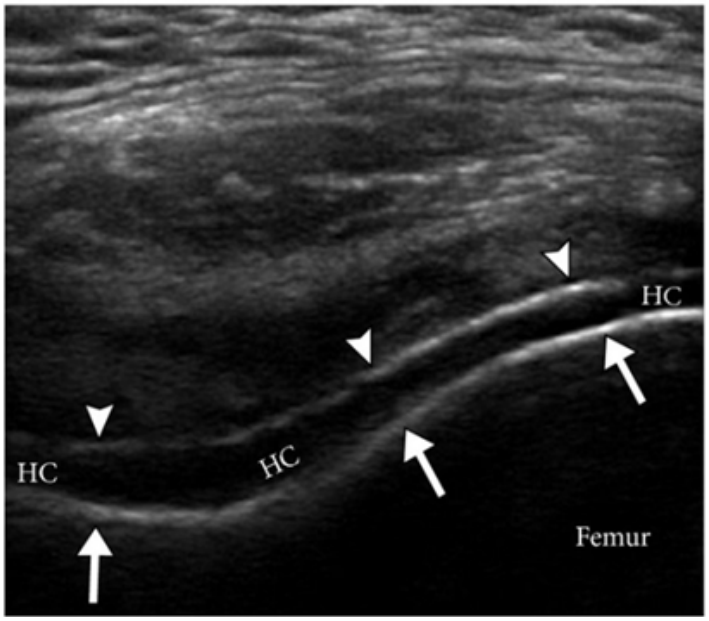


Figure 4: Suprapatellar maximal flexion transverse view of the knee on POCUS showing the double contour sign. Arrows = femoral cortex, arrowheads – deposition of monosodium urate above the hyaline cartilage (HC)

Attribution

Girish G, Melville DM, Kaeley GS, et al. Imaging appearances in gout. Arthritis. 2013;2013:673401. doi: 10.1155/2013/673401. Epub 2013 Mar 25. PMID: 23585966; PMCID: PMC3621383.

Dual energy computed tomography (DECT) can be helpful noninvasive alternative to arthrocentesis to see monosodium urate crystals (Figure 5). However, its limited availability makes POCUS a more widely accessible and still a noninvasive tool for this purpose.

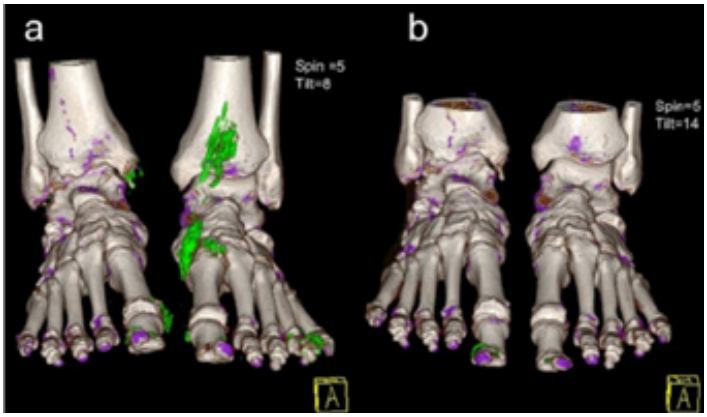


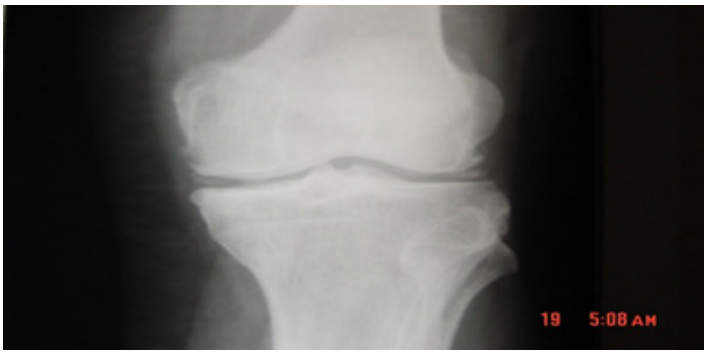
Figure 5: 3-dimensional DECT reconstruction images (a. pre-treatment; and b. 16 months after treatment with urate lowering therapy); please note complete resolution of the tophi [Green: MSU deposits; Purple: calcium; A: anterior].

Attribution

Jayakumar D, Sehra ST, Anand S, Stallings GW, Danve A. Role of Dual Energy Computed Tomography Imaging in the Diagnosis of Gout. Cureus. 2017 Jan 20;9(1):e985. doi: 10.7759/cureus.985. PMID: 28229032; PMCID: PMC5318147.

Pseudogout

Calcium pyrophosphate dihydrate crystals can get deposited in various parts of the skeleton and associated structures, inciting inflammation and resulting in the various clinical manifestations of pseudogout. Typically, calcification of the triangular fibrocartilaginous complex in the wrist can be picked up on plain radiographs or on POCUS. Chondrocalcinosis of the hyaline articular cartilage lining the femur can also be picked up on plain radiographs (Figure 5); while on POCUS the classic finding is that of intra-substance hyaline articular cartilage and/or in the menisci (Figure 6).



Courtesy: Prof. Anand N. Malaviya, India

Figure 6: Chondrocalcinosis in the knee/knee joint - commonly seen in CPPD crystal disease.

Rowned-dens syndrome is a rare manifestation of pseudogout typically seen in the elderly where they might present acutely with severe neck pain typically localized to the base of the skull, constitutional symptoms like fever and chills and clinical signs that could be suggestive of meningitis; however, a CT scan of the skull and upper cervical spine shows a classic ring of calcification around the odontoid process of the second cervical vertebra**.** The treatment is very gratifying with corticosteroids leading to a rapid relief and recovery.

Basic Calcium Phosphate Disease/Hydroxyapatite Arthropathy

In young individuals, especially women, it can present with intermittent episodes of acute inflammatory affliction of the ankle area which subsides completely over a few days with minimal therapeutic intervention like nonsteroidal anti-inflammatory agents just to come back later. During the episodes, plain radiographs of the ankle joint can show radiopaque densities around the ankle joint suggestive of ankle periarthritis. Mysteriously, as these crystals get reabsorbed by the body, during the intercritical phase, plain radiographs of the same joint are free of these radiopaque densities!

In the elderly, especially in women, more so reported in the colder states of the upper Midwest, basic calcium phosphate arthropathy can lead to rapidly destructive arthritis of the glenohumeral joint with a hemorrhagic effusion, typically termed as Milwaukee shoulder. Aspiration of the afflicted joint followed by analysis of the synovial fluid with special Alizarin-red stain can show the crystals of basic calcium phosphate/hydroxyapatite which are typically not birefringent on polarized microscopy.

Polymyalgia rheumatica (PMR)

It is a systemic inflammatory disease that typically starts after the age of 50 with bilateral shoulder/pectoral girdle and pelvic girdle achiness. The ACR classification criteria now have 2 wings for PMR - with ultrasound and without ultrasound. In the ultrasound wing, glenohumeral synovitis, bicipital tenosynovitis and subacromial/subdeltoid bursitis are included for the shoulder, and coxofemoral/hip joint synovitis and trochanteric bursitis are included for the hip evaluation sonographically [8]. This has definitely increased the value of POCUS in diagnosing PMR. The treatment of PMR is very gratifying with a relatively low dose of prednisone ranging from 10 to 20 mg a day causing a miraculous improvement in symptoms within a very short period of time that can range from hours to a day or two. The challenge comes with the sibling entity of giant cell arteritis (GCA) that can affect up to 15% patients with PMR. GCA is a large vessel systemic vasculitis, the commonest vasculitis in North America, and can lead to irreversible loss of vision as well as mortality if not diagnosed and hence treated in a timely fashion. Of course, in addition to clinical examination/evaluation with a typical history of amaurosis fugax, jaw claudication and new onset left severe headache, along with elevation in acute phase reactants, ultrasonographic findings of a halo around the temporal artery (Figure 7) has been found to be very helpful towards diagnosing this condition in a timely fashion and even towards directing the need of a temporal artery biopsy which has

been considered to be the gold standard diagnostic tool for GCA.

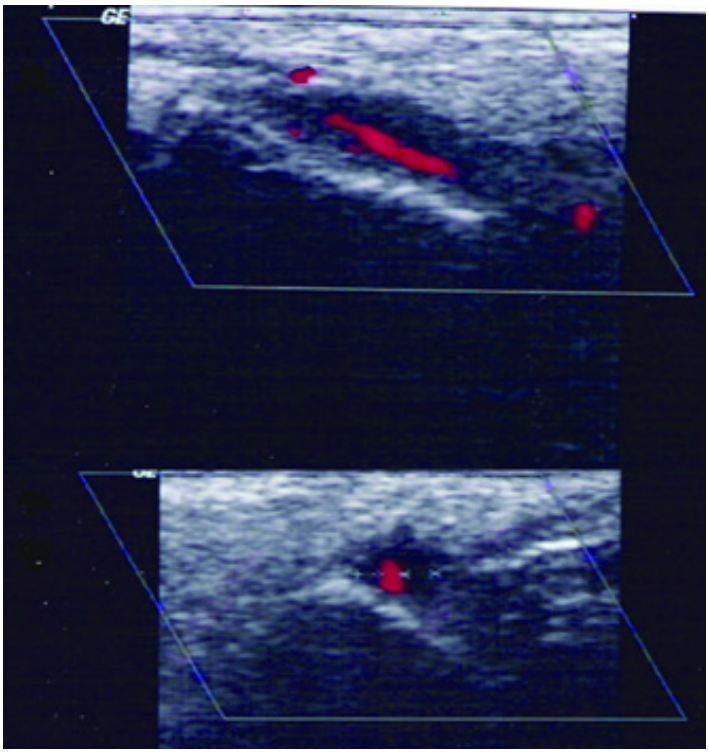


Figure 7: Giant cell arteritis. Color-Doppler sonography demonstrating the 'halo sign' as the hypoechoic area around the temporal artery in longitudinal (upper panel) and transverse (lower panel) views.

Attribution

Karahaliou M, Vaiopoulos G, Papaspyrou S, et al. Colour duplex sonography of temporal arteries before decision for biopsy: a prospective study in 55 patients with suspected giant cell arteritis. Arthritis Res Ther. 2006;8(4):R116. doi: 10.1186/ar2003. PMID: 16859533; PMCID: PMC1779378.

Positron emission tomography (PET) can be helpful especially with the large-vessel-only variant of GCA, where it can show aortitis or arteritis of some major arteries including yet not limited to the subclavian arteries (Figure 8).

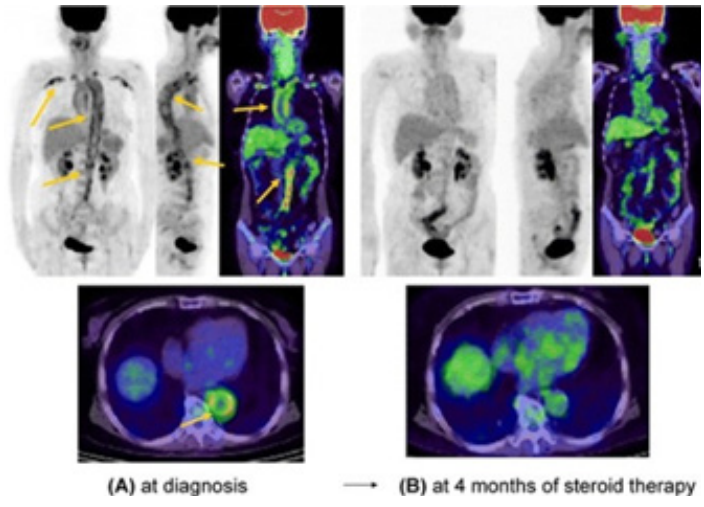


Figure 8: Large vessel vasculitis: 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) images identifying (A) thoracic and abdominal aortitis and bilateral subclavian and subclavian arteritis; (B) Update went down markedly post corticosteroid therapy.

Attribution

Yamashita H, Kubota K, Mimori A. Clinical value of whole-body PET/CT in patients with active rheumatic diseases. Arthritis Res Ther. 2014;16(5):423. doi: 10.1186/s13075-014-0423-2. PMID: 25606590; PMCID: PMC4289312.

Pulmonary and renal involvement in systemic inflammatory RMD

HRCT of the lungs can show classic ground glass opacities suggestive of active interstitial lung disease or honeycombing/ other features of fibrotic pulmonary parenchymal involvement. Interventional radiology (IR) offers assistance with renal biopsy has come as a very helpful tool for diagnosing and classifying glomerulonephritis in diseases like SLE. Focal proliferative glomerulonephritis (class III) lupus nephritis and diffuse proliferative glomerulonephritis (class IV) lupus nephritis require aggressive management with various immunosuppressive therapies for a favorable outcome. In antineutrophil cytoplasmic antibody (ANCA) associated vasculitides, IR-led kidney biopsy helps visualize pauci-immune glomerulonephritis with or without crescents, thereby leading to timely management of a serious medical condition, granulomatosis with polyangiitis (GPA) that used to be considered a death sentence until the advent of use of cyclophosphamide four decades or so ago. It is now possible for patients with ANCA associated vasculitides, including GPA to lead a fulfilling life with early management. That is very comforting! Other pulmonary renal syndromes including Goodpasture's disease are also helped by IR-led renal and/or other organ-biopsy.

Central Nervous System (CNS) Vasculitides

This group of diseases can be very challenging both diagnostically and hence therapeutically. CT/MR angiogram of the brain with the classic 'string of beads' appearance (alternating areas of stenosis and dilatation) (Figure 9) has been very helpful. IR-assisted leptomeningeal biopsy is the gold standard for the diagnosis of this condition which can be associated with a significant degree of morbidity and mortality if not diagnosed and hence treated in a timely fashion with various immunosuppressive modalities.

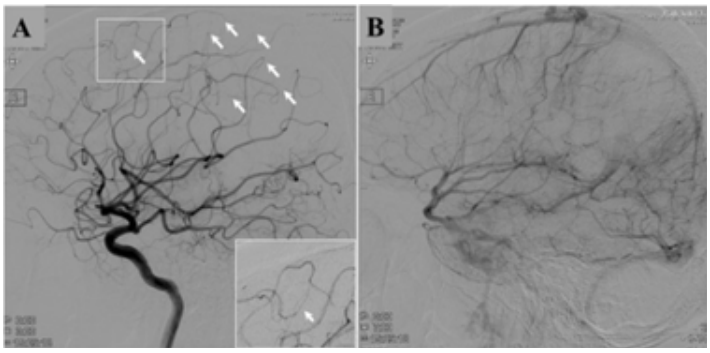


Figure 9: CNS vasculitis. Right internal carotid angiography. A. Arterial phase showing multiple segmental narrowing (arrows) of the distal part

of the anterior cerebral artery and middle cerebral artery. B. Venous phase of angiography revealing multiple venous occlusions in the right parietal area.

Attribution

Gekka M, Sugiyama T, Nomura M, Kato Y, Nishihara H, Asaoka K. Histologically confirmed case of cerebral vasculitis associated with Crohn's disease--a case report. BMC Neurol. 2015 Sep 21;15:169. doi: 10.1186/s12883-015-0429-7. PMID: 26390922; PMCID: PMC4578610.

Carpal Tunnel Syndrome/Entrapment of Median Nerve at the Level of the Wrist

It can result from a number of conditions including chronic inflammation of the carpus/wrist from RA/PsA/crystal arthritides etc. or it can be primary/idiopathic. Pregnancy, hypothyroidism, acromegaly etc. or other associations etiologically. Traditionally electromyogram/nerve conduction studies have remained the mainstay of diagnosing this condition. However, using POCUS, it is now possible to make a diagnosis of the entrapment of the median nerve at the level of the entrance to the carpal tunnel using a single view called the volar transverse view of the wrist. Typically, a high-frequency probe with the correct footprint-size is used. Cross-sectional area of the median nerve is measured in this view where scaphoid bone forms the radial/lateral boundary, the pisiform bone forms the medial/ulnar boundary, the lunate and triquetrum bones form the floor while the flexor retinaculum forms the roof for the carpal tunnel. Typically, a cross-sectional area of the median nerve on this view greater than 0.12 cm^2, in conjunction with compatible clinical features, a diagnosis of carpal tunnel syndrome can be made with a fairly high degree of certainty [9].

Osteoarthritis

Plain radiographs of the hands typically show 'gullwing' changes in the distal interphalangeal joints corresponding to the clinical findings of Heberden's nodes and in the proximal interphalangeal joints corresponding to the clinical findings of Bouchard's nodes in erosive osteoarthritis that is typically seen in middle-aged to older women and tends to follow a maternal to daughter transmission. Similar findings can be seen in advanced systemic sclerosis also.

Joint-space narrowing with osteophytes of the first carpometacarpal joint/the trapeziometacarpal joint is quite classic of osteoarthritic involvement because this joint is typically spared by RA, PsA and other inflammatory arthritides. Of the large joints, asymmetrical joint space narrowing of the knee joint with a propensity to involve the medial compartment more than the lateral compartment accompanied by subchondral sclerosis, osteophytes and 'geodes' is quite classic of osteoarthritis. Joint space narrowing is typically asymmetrical and osteoarthritis compared to rheumatoid arthritis. Osteoarthritis of the spine can involve the cervical, lumbar and to a lesser extent the thoracic segments. Osteophytes in the spine are typically asymmetrical and horizontal compared to the vertically growing syndesmophytes seen in Ax SpA. 'Vacuum sign' of the intervertebral disc space is also a feature of osteoarthritis. SIJ are typically spared by osteoarthritis unlike Ax SpA.

IgG-4 related disease (IgG-4 RD)

It is a relatively recent revelation in the realm of Medicine. Aortitis, retroperitoneal fibrosis, submandibular and lacrimal gland involvement, recurrent acute pancreatitis, hypophysitis etc. are just some of the myriad clinical features of this entity. MRI and 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (PET/CT) scan can be helpful diagnostically in Sjogren's disease [SD] as well as IgG-4 RD (Figure 10). The latter can also help gauge response to therapy typically with corticosteroids and immunosuppressants including rituximab.

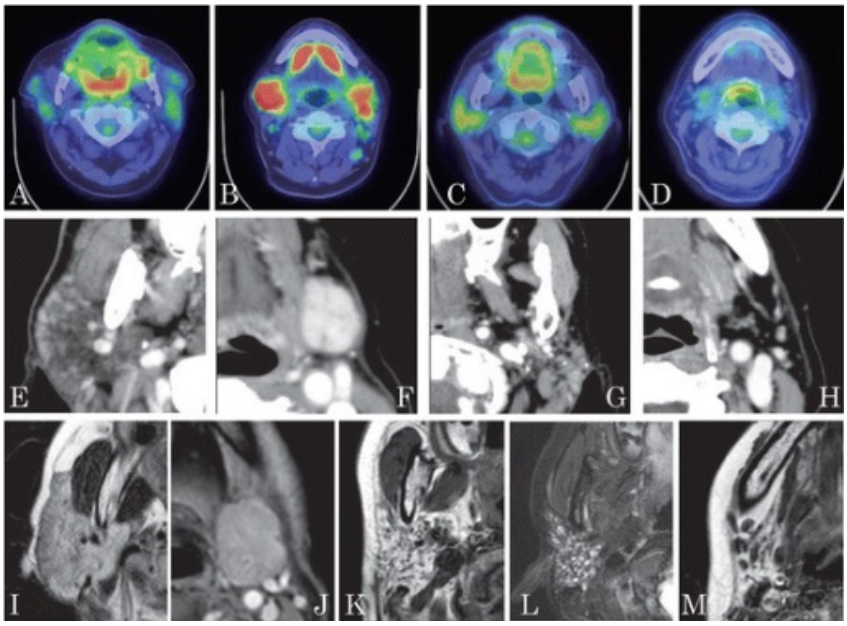


Figure 10: IgG-4 RD. FDG-PET/CT (A-D), CT (E-H) and T2-weighted MRI (I-M). Sialedenitis of the parotid and submandibular glands in IgG4-RD and SD.

Attribution

Shimizu M, Okamura K, Kise Y, Takeshita Y, et al. Effectiveness of imaging modalities for screening IgG4-related dacryoadenitis and sialadenitis (Mikulicz's disease) and for differentiating it from Sjögren's syndrome (SS), with an emphasis on sonography. Arthritis Res Ther. 2015 Aug 23;17(1):223. doi: 10.1186/s13075-015-0751-x. PMID: 26298875; PMCID: PMC4546818.

Hemochromatosis

It is one of those exceptions where premature osteoarthritis tends to involve the metacarpophalangeal (MCP) joints, which are typically spared by osteoarthritis by and large. Usually it is the patient's dominant hand's second and third MCP joints that show large hook like radial osteophytes. Accompanying clinical features including a brown skin, hepatic function derangement, hypogonadism, congestive heart failure and diabetes typically in a young to middle-aged male of northern European descent; accompanied by pertinent laboratory testing including elevated serum ferritin and gene mutation including C282Y (the most common), H63D and S65C can clinch the diagnosis. Females tend to get spared by this disease due to the menstrual blood/iron loss every month but can get it postmenopausally.

Multicentric Reticulohistiocytosis (MRH)

In this rare disease, rapid destruction especially of the distal interphalangeal (DIP) joints of the hands can be picked up radiographically. The involvement of the DIP joints is unique to some very specific diseases including primary nodal osteoarthritis (as discussed above), a subset of PsA (as discussed above), juvenile form of RA, Still's disease and MRH. The presence of waxy papules/nodules of the skin overlying the afflicted joints in the absence of classic biomarkers of RA can help substantiate the diagnosis. There is an association of MRH with visceral malignancies.

Sarcoidosis

Plain radiography of the chest can give hints towards hilar adenopathy, mediastinal adenopathy as well as pulmonary parenchymal involvement. HRCT of the chest can provide further fine details. Gallium-67 nuclear scan can show a classic 'panda sign' (abnormal uptake in bilateral parotid and lacrimal gland combined with normal uptake in the nasopharyngeal mucosa). Gallium-67 scintigraphy or PET scanning can show the 'lambda sign' (prominent right paratracheal area with bilateral hilar and mediastinal lymphadenopathy), which is quite specific. IR can be very helpful with getting a tissue sample from hilar/mediastinal lymphadenopathy classically showing noncaseating granulomas.

Osteoporosis

It is a condition that is managed by primary care physicians, endocrinologists and certain rheumatologists. Low bone mass (previously called osteopenia) and osteoporosis can be diagnosed on dual-energy x-ray absorptiometry (DXA) scan. The International Society of clinical densitometry does offer certification in this regard. Spinal, hip and peripheral/radial densitometry can be used for this purpose. The 10-year risk of a major osteoporotic fracture can be calculated accordingly using an algorithm/FRAX score **https://frax.shef.ac.uk/FRAX/**.

Conclusion

Imaging remains a very helpful tool in the diagnosis, management and follow-up of rheumatic diseases.

Acknowledgment/Disclosure

Authors acknowledge and express gratitude for the images obtained from The National Institute of Health's Open "i" site (Open Access Biomedical Image Search Engine); License type: Attribution. The PubMed reference for each such image/picture has been acknowledged with the image itself. There have been no changes made in the images thus obtained.

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