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CASE REPORT

Fever of Unknown Origin with Fluorodeoxyglucose-crowned Dens Syndrome on Positron Emission Tomography: Case Reports

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INTRODUCTION

The term crowned dens syndrome (CDS) was coined four decades ago to first describe acute neck pain with calcium crystal depositions that showed a crown-like density surrounding the odontoid process (dens) on frontal-view radiographs.[1] CDS remains an uncommon condition that is often misdiagnosed as other infective, inflammatory, or neoplastic disorders.[2] It has been increasingly recognised as a peculiar manifestation of calcium pyrophosphate deposition (CPPD) disease in the aged population.[3] We describe two patients with CDS and an unusual constellation of clinicoradiological features who were investigated for fever of unknown origin (FUO) by both gallium-67 scintigraphy and fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT). Only the latter revealed the diagnosis based on a rarely reported imaging pattern.

CASE 1

An 82-year-old woman was admitted for biliary sepsis complicated by hospital-acquired pneumonia. She underwent endoscopic intervention and was prescribed broad-spectrum antibiotics. Recurrent intermittent fever persisted for 4 weeks with raised leucocyte count (17×10^9/L), erythrocyte sedimentation rate (>100 mm/h), and C-reactive protein level (130 mg/L). The patient had no localising symptoms. Gallium-67 scintigraphy for FUO reported resolving pneumonia with mild activity but could not localise other sources of infection. Her fever persisted for another 4 weeks. Torso FDG PET-CT was then performed. PET revealed polyarticular FDG hyperactivity (maximum standardised uptake values [SUVmax] 3.3-6.3) involving the shoulder, sternocostoclavicular, wrist, lumbar apophyseal and sacroiliac joints, and a characteristic pattern (SUVmax 4.0) around the dens of axis (Figure 1). CT detected subtle, mottled high-attenuation deposits in retro-odontoid soft tissues, and more deposits in the shoulder and sternoclavicular articulations, and in the pubic symphysis where it had no hyperactivity. Gallium-67 images were reviewed and considered to show no abnormal uptake in the cervical spine (Figure 2). The patient was diagnosed as a probable case of CPPD disease solely based on FDG PET-CT. She was prescribed colchicine and low-dose prednisolone with rapid resolution of pyrexia and inflammatory markers.

CASE 2

A female nonagenarian had a history of CPPD disease

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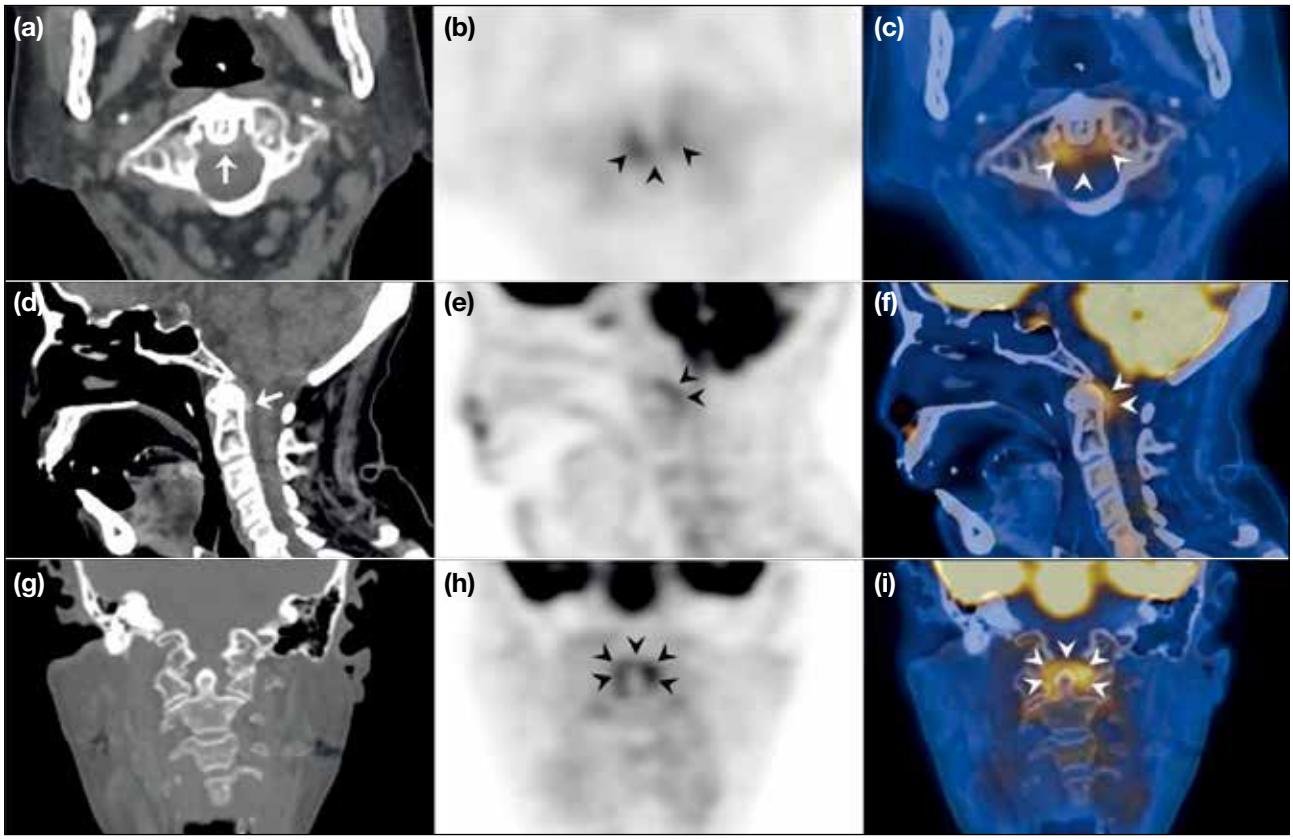

Figure 1. Case 1. Fluorine-18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) with (a-c) axial CT, PET and fused PET-CT images, (d-f) sagittal CT, PET and fused PET-CT images, and (g-i) coronal CT, PET and fused PET-CT images of the atlantoaxial region. PET and fused images showing a characteristic pattern of FDG hyperactivity (maximum standardised uptake value 4.0) crowning the dens of C2 vertebra (arrowheads). CT images showing a few subtle, mottled high-attenuation deposits in retro-odontoid soft tissues or the transverse ligament of C1 vertebra (arrows).

Figure 2. Case 1. Gallium-67 single-photon emission computed tomography–computed tomography (SPECT-CT) with (a) axial, (b) sagittal, and (c) coronal fused SPECT-CT images of the atlantoaxial region showing no abnormal gallium uptake around the odontoid process of C2 vertebra (asterisks).

proven by knee synovial fluid analysis. She had repeat admissions for pneumonia and septicaemia. Her episodes evolved into FUO despite extensive workup and prolonged courses of antibiotics. Gallium-67 scintigraphy demonstrated polyarticular uptake, especially at the shoulders and knees. Cervical spine had no abnormal gallium uptake. She underwent image-guided shoulder arthrocentesis that yielded negative cultures and no crystals. Her fever persisted on and off for another 6 weeks. FDG PET-CT was then performed and confirmed polyarthropathy with hyperactivity (SUVmax 2.8-4.8) over the shoulders, sternoclavicular junctions, pubic symphysis, knees, and with a characteristic pattern (SUVmax 3.7) around the dens (Figure 3). She was prescribed colchicine and made a rapid recovery.

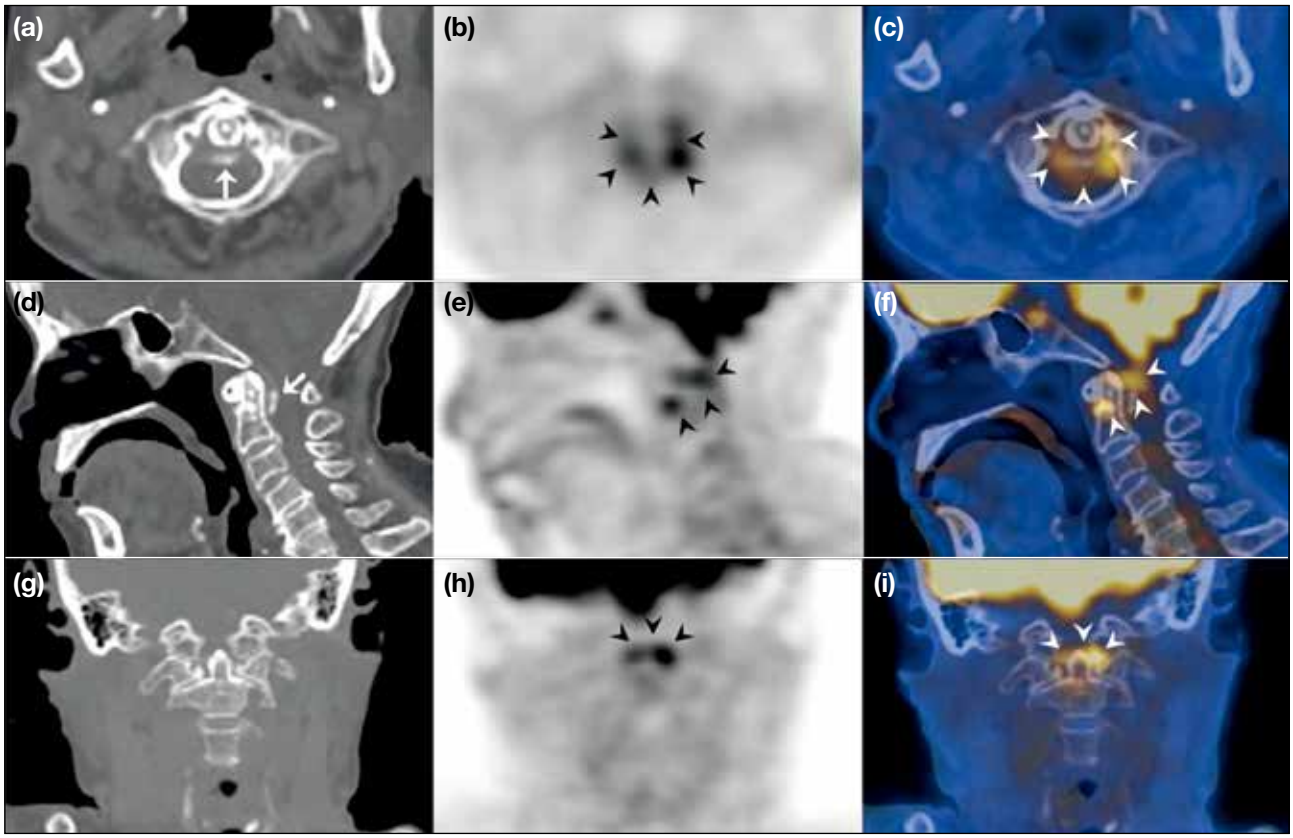

Figure 3. Case 2. Fluorine-18 fluorodeoxyglucose positron emission tomography–computed tomography (FDG PET-CT) with (a-c) axial CT, PET and fused PET-CT images, (d-f) sagittal CT, PET and fused PET-CT images, and (g-i) coronal CT, PET and fused PET-CT images of the atlantoaxial region. PET and fused images showing a characteristic pattern of FDG hyperactivity (maximum standardised uptake value 3.7) surround the odontoid process of C2 vertebra in posterior, posterolateral, and lateral aspects (arrowheads). CT images showing a curvilinear or arc-shaped periodontoid calcification in the region of transverse ligament (arrows).

DISCUSSION

CDS is an uncommon but important condition encountered by many specialties. Approximately 320 cases were found in the English literature. It remains a clinicoradiological entity but with a widening spectrum, characterised by locoregional features (e.g., neck pain, neck rigidity, headache, shoulder pain), inflammatory response (pyrexia, leucocytosis, elevated erythrocyte sedimentation rate, C-reactive protein level), and calcium crystal deposition at and around the atlantoaxial articulations evident as periodontoid calcifications on CT.[1,2,4-6] Nonetheless there is no consensus on diagnostic or inclusion criteria, hence a wide variation of reported presentations, e.g., local symptom onset varies as acute, subacute, chronic, periodic or uncertain; pyrexia is present or absent; inflammatory markers are normal or elevated; and rare features such as meningeal signs or cervical myelopathy. FUO is also rarely reported, mimicked by cases of prolonged evolution with relapses.[2,4] The two cases we describe shared a common course: both were elderly patients with a prolonged severe infective illness that could cause flare-up of underlying CPPD disease with CDS, and evolve into FUO without overt localising sources other than generalised deconditioning. Such a clinical scenario for CDS is underreported.

The radiological part of CDS, calcium crystal deposition evident on CT, is the cornerstone and present in virtually every reported case. It may have led to better recognition of CDS, even when asymptomatic, in patients with CPPD disease.[4,6] Nonetheless such CT findings may also be common in the elderly people with no CPPD disease history. The prevalence of "incidental" periodontoid calcifications on CT has been reported in the United States to be 34% in those aged ≥60 years, and 49% for those aged ≥80 years.[7] Corresponding prevalences of 15% and 24% have been reported in Japanese patients.[8] The

prevalence of "concomitant" periodontoid calcifications with or without neck symptoms in CPPD patients has been reported as 51% to 63%.[4,6,8] These prevalence data in non-CPPD and CPPD patients highlight the importance of other criteria such as pyrexia or inflammatory markers in making a diagnosis of CDS, especially in the elderly people.[7]

The use of FDG to image infection and inflammation is widely accepted.[9] It can localise occult sources and delineate extent and severity. FDG hyperactivity at and around atlantoaxial articulations is strong evidence of an active inflammatory process in vivo, constituting the metabolic (inflammatory) form of structural abnormalities on imaging. To the best of our knowledge, only six cases of CDS with PET-CT have been recently reported (five in English, one in Dutch).[10-12] We report two additional cases, highlighting a characteristic pattern of FDG hyperactivity crowning the dens, best shown on axial or coronal planes. Hyperactivity was of a mild-to-moderate degree. We propose the presence of periodontoid FDG hyperactivity (higher than adjacent background activity), conforming to the "FDG-crowned dens" pattern, to be included as one of the criteria for CDS, equivalent to periodontoid calcifications on CT. This notion awaits further research or more reported CDS with PET-CT features.

With reference to other radionuclide studies, four CDS cases have been published with positive technetium-99m diphosphonate bone scintigraphy. The mechanism of diphosphonate uptake is chemisorption onto bone surface and calcium crystals. This should aptly correspond to periodontoid calcifications and any subchondral bony changes secondary to degeneration or inflammation, thus giving only little additional information to CT alone. Bone scintigraphy is nonetheless helpful to detect polyarthropathy or polyostotic disease. There was no reporting of gallium-67 in the literature on CDS. Gallium-67 scintigraphy was conventionally used to investigate FUO.[13] Nonetheless its spatial resolution and contrast sensitivity are poorer than that of PET-CT. This may explain the negative gallium-67 scintigraphy in the above cases despite a subsequent positive PET-CT, particularly when the degree of inflammation during asepsis was not as florid as that due to septic arthritis.

The aetiology of CDS is calcium pyrophosphate (CPP) and/or basic calcium phosphate (BCP, mostly hydroxyapatite) crystal deposition. CPP crystals preferentially deposit in articulations (synovial fluid, hyaline cartilage, fibrocartilage, ligament, synovium, capsule). BCP crystals are frequent in articular and extra-articular tissue, especially tendons and soft tissue. At the atlantoaxial region, CPP crystals deposit in periodontoid structures, most frequently in transverse ligament of the atlas posterior to dens of the axis, whereas BCP crystals may also deposit in the longus colli tendon anterior to dens. CDS is most frequently due to CPPD disease that has a broad spectrum including asymptomatic CPPD disease in the elderly people, osteoarthritis with CPPD, acute CPP crystal arthritis (formerly referred to as pseudogout), and chronic CPP crystal inflammatory arthritis.[3] Nonetheless CDS can also be related to hydroxyapatite deposition disease that more often affects adult females with a favourable outcome of calcium resorption,[14] or be reported in rheumatoid arthritis, seronegative spondyloarthritis, systemic sclerosis, and osteoarthritis.[15] Therefore, CDS is not pathognomonic of CPPD disease and further exploration of articular and peri-/extra-articular sites is required to determine the underlying disease. FDG PET-CT can evaluate inflammatory lesions in the body and help direct further investigation at the most severe and accessible sites and may differentiate CDS from other conditions. Lastly, imaging methods per se do not establish with absolute certainty the type of crystal involved. A definitive diagnosis of CPPD disease is based on the presence of CPP crystals in synovial fluid or biopsied tissue.

Differential diagnoses for CDS encompass meningitis, epidural abscess, cervical spondyloarthritis, polymyalgia rheumatica, temporal arteritis, and neoplastic or metastatic disease.[2,4] Prior injury, surgery, and severe intercurrent illness may cause underlying CPPD disease to flare up.[3] The clinician should be constantly vigilant for preceding or concomitant infection. In many reported cases, a timely diagnosis of CDS can avoid invasive investigations such as lumbar puncture, temporal artery biopsy, or surgical exploration. CDS should typically demonstrate dramatic improvement when treated with non-steroidal anti-inflammatory drugs or colchicine and, if clinically indicated, low-dose corticosteroids. An early diagnosis of CDS is thus important to allow effective treatment and avoid prolonged hospitalisation.

CONCLUSION

CDS remains an uncommon clinicoradiological entity with a wide spectrum of presentations including FUO. CT has been the cornerstone of diagnostics but periodontoid calcifications per se may not always be associated with

inflammation and may be prevalent in extreme elderly people without disease. The characteristic metabolic pattern of "FDG-crowned dens" is rarely recognised but is strong evidence of active inflammation in vivo, thereby helping to confirm CDS and leading to effective treatment. We propose that this imaging pattern be included as one of the criteria for CDS to heighten physician awareness. With increasing use of PET-CT for FUO, more cases may be detected, although whether this will help refine diagnostic criteria or define subsets awaits further research.

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