

CASE REPORT

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## A case of Castleman's disease associated with diffuse idiopathic skeletal hyperostosis and ossification of the posterior longitudinal ligament of the spine

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**Abstract** Castleman's disease (CD), diffuse idiopathic skeletal hyperostosis (DISH), and ossification of the posterior longitudinal ligament of the spine (OPLL) are three different entities. Castleman's disease displaying a variety of calcifications in the abdomen and/or pelvis has been reported in some papers. However, there were no reports suggesting an association between CD and ossification/calcification in spine and joints. So far, there has been no case report regarding the coexistence of these diseases in the literature. Herein, we detail a 75-year-old man suffering from CD who demonstrated the features of DISH with coexisting features of OPLL. The cardinal symptoms such as fatigue, high fever, and swollen glands in this case were reduced by corticosteroid therapy. However, it is possible to produce actual symptoms of ossifying/calcified diathesis of entheses and ligaments as a consequence, like the pathology of calcification found in the region of the spleen. In this paper, we describe this patient in order to discuss the association of these diseases.

**Key words** Calcification · Castleman's disease · Diffuse idiopathic skeletal hyperostosis (DISH) · Ossification of the posterior longitudinal ligament of the spine (OPLL)

### Introduction

Castleman's disease (CD), in which Castleman initially described a patient with many years of fever and weakness and a large mediastinal mass, is a rare disorder characterized by noncancerous growths that may develop in the lymph node tissue throughout the body.<sup>1,2</sup> There are two

main types of CD: hyaline-vascular type and plasma cell type.<sup>2</sup> Moreover, the recognition of both patients with localized lymphadenopathy and disseminated disease led to an additional clinical categorization of CD: "unicentric" (UCD) versus "multicentric" (MCD).<sup>2</sup>

Most recently, a third type of CD, known as plasmablastic MCD, has been described in association with particularly aggressive cases of MCD. In the first series to describe such a variant, CD patients with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes) were found to have lymph nodes which resembled those in the plasma cell variant, but also had large plasma cells in the mantle zone with copious cytoplasm and prominent single or multiple nucleoli.<sup>3,4</sup> A second series found the variant to be associated with HHV-8 infection and progression to plasmablastic lymphoma.<sup>5</sup>

Diffuse idiopathic skeletal hyperostosis (DISH), on the other hand, is a systemic noninflammatory disorder that might be classified as ossifying/calcified diathesis of entheses and ligaments.<sup>6</sup> Ossification/calcification starts and extends from insertions of skeletal muscles, ligaments, and joint capsules. The most prominent features of DISH appear on the spine as flowing appositions of newly formed ectopic bone along the anterolateral aspect of the spine. Moreover, ossification of the posterior longitudinal ligament of the spine (OPLL) also involves the posterior aspect of vertebral bodies and discs, predominantly of the cervical spine.<sup>7</sup> A varying proportion of patients with DISH have OPLL, and vice versa.<sup>8</sup>

Until now, CD displaying a variety of calcifications in the thorax, abdomen, and/or pelvis has been reported.<sup>9–12</sup> However, to our knowledge, there were no reports suggesting an association between CD and ossification/calcification, and CD with diffuse DISH and OPLL has not been reported in the English literature. In this paper we report a 75-year-old man suffering from CD with diffuse DISH and OPLL.

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## Case report

A 75-year-old HIV-negative Japanese man had been in excellent health until June 1996, when he was suffering from fatigue, dry cough, night sweat, loss of appetite, continuous high fever, and body weight loss with severe anemia from July 1996. He also had polyarthralgia in bilateral hands. In January 1997, the patient presented to our hospital because there was no improvement regardless of treatment.

On physical examination the patient was afebrile and appeared well. Liver and spleen were not palpable. However, multiple lymph nodes were swollen and palpable on cervical, under the jaw, behind the ears, in the axillary, and in the groin.

Laboratory tests disclosed increased serum total protein (10.4 g/dl) with hypoalbuminemia and a normochromic anemia, with a hemoglobin (Hb) count of 7.8 g/dl and a red blood cell (RBC) count of  $276 \times 10^4$ , although the white blood cell (WBC) count was 6200 with a normal differential count. Serum immunoelectrophoresis showed high levels of serum polyclonal immunoglobulins (IgG) (6852 mg/dl). Although the erythrocyte sedimentation rate (ESR) (117 mm/30 min) and C-reactive protein (CRP) level (1.3 mg/dl) were elevated, the lactate dehydrogenase (LDH) level was low (263 IU/ml). Immunologic tests for hepatitis B and C were negative. Evaluation of the RAHA test was  $\times 640$ , and antinuclear antibody (ANA) was  $\times 1280$ . Proteinuria was 2+. Serum levels of interleukin-6 (IL-6) (7.84 pg/ml) were elevated.

A thoracic, neck, and abdominal computed tomography (CT) scan showed multiple lymph nodes. Histological findings from lymph node in the groin were consistent with a diagnosis of CD, manifesting as follicular hyperplasia, hypervascularity, and few plasma cells in the interfollicular stroma.

This patient's disease was diagnosed as multicentric CD by clinical symptoms, laboratory data, and histological findings by an excision lymph node biopsy. Oral prednisolone was administered at 60 mg/day from February 27, 1997 for 2 weeks, and tapered to 5 mg/week by 3 months; thereafter it was maintained ranging from 10 to 15 mg daily. Three months after the start of prednisolone therapy, the patient's symptoms disappeared and his Hb (14.9 g/dl), ESR (10.1 mm/h), serum CRP (0.1 mg/dl), lactate dehydrogenase (161 IU/ml), IgG (992 mg/dl), ANA  $\times 40$ , and IL-6 (1.98 pg/ml) levels showed improvement. His clinical symptoms disappeared, and the lymphadenopathy had resolved completely. However, an abdominal CT examination showed a focal calcification in the region of the spleen (Fig. 1).

During the follow-up period of 10 years, disease activity of CD was relatively well controlled; however, the patient had intermittent pains in the neck and lower back from around 2000. Physical examination revealed significant cervical paraspinal muscle spasm, and reduced range of motion to flexion and extension of the cervical spine. There were no neurological abnormal signs. A dense band of ossification was radiographically noted along the posterior

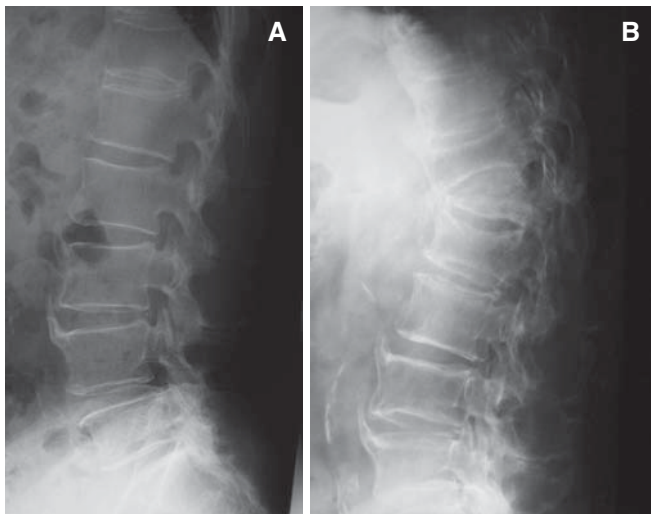


**Fig. 1.** Abdominal computed tomography examination showed a focal calcification in the region of the spleen (arrow)



**Fig. 2.** A dense band of ossification was radiographically noted along the posterior aspect of the C2-3. Mild disc space narrowing was noted at C2-3 and C3-4. From these findings, ossification of the posterior longitudinal ligament of the spine (OPLL) was diagnosed

aspect of the cervical vertebral bodies. Mild disc space narrowing was noted at C2-3 and C3-4 (Fig. 2). From these findings, ossification of the posterior longitudinal ligament of the spine (OPLL) was diagnosed. Until the present time, diabetes mellitus has never been diagnosed in this patient. Additionally, radiographic findings of the thoracolumbar spine revealed large bridging anterior osteophytes from the lower thoracic spine to the level of L4 (Fig. 3A). Moreover, the patient had complaints of pain around both ankle joints. A plain radiogram of the ankles showed large osteophytes



**Fig. 3.** **A** In 1999, radiographic findings of the thoracolumbar spine revealed large bridging anterior osteophytes from the lower thoracic spine to the level of L4. **B** In 2006, three thoracolumbar vertebral body (T11, T12, and L1) fractures were observed



**Fig. 4.** Radiographic findings of calcaneus showed osteophytes at the calcaneal base and the insertion of the Achilles tendon, and in particular there was obvious ossification of the right Achilles tendon (arrow)

at the calcaneal base and a distal posterior calcaneal lesion, and there was obvious ossification/calcification of the right Achilles tendon (Fig. 4). From these radiological findings, diffuse idiopathic skeletal hyperostosis (DISH) was diagnosed.

He also had severe pain in both knee joints and had undergone total knee arthroplasty in August 2006. The pathological findings of the synovial tissue showed little inflammatory change with lymphoplasmacytic infiltration. No crystal deposition in the capsule or synovium was found. After the operation, his condition was satisfactory, but he had severe back pain again caused by compression fracture of the thoracic vertebrae and osteoporosis. Three thoracolumbar vertebral body (T11, T12, and L1) fractures were observed (Fig. 3B). Treatment with the bisphosphonate alendronate was used for the multiple vertebral compression fractures.

## Discussion

Castleman's disease in the abdomen and pelvis is most commonly described in the radiology literature as a focal enhancing mass of varying locations, including the retroperitoneum, mesentery, porta hepatis, and pancreas.<sup>9,10</sup> A focal mass in the abdomen and pelvis displays a variety of calcification patterns, including punctate, coarse, peripheral, and "arborizing."<sup>9-12</sup> Sadamoto et al. reported a 22-year-old female patient with retroperitoneal CD of the hyaline vascular type presenting with arborizing calcification.<sup>13</sup> Goetze et al. reported that an asymptomatic case of unicentric, hyaline, vascular-type CD localized to the tail of the pancreas with central calcification.<sup>14</sup>

Meador and McLarney reported that 15 patients (94%) among 16 CD patients were found to have a single mass on CT, and calcification was seen in five (31%); punctate calcification was seen in four patients and an "arborizing" or radial pattern of calcification was seen in one patient.<sup>9</sup> In this case, the lymphadenopathy had resolved completely by the treatment of high-dose steroid. Therefore, it was thought that a focal mass of calcification in the abdomen and pelvis could not be found except for a focal calcification in the spleen. However, there is a possibility that ossification similar to the pathology of calcification described above appeared.

Otherwise, it is not yet clear whether DISH and OPLL are genetically related.<sup>8</sup> Despite a series of clinical, X-ray, and laboratory investigations, the cause and pathogenesis are still unsolved, both in DISH and in OPLL. The principal question of possible genetic relations between DISH and OPLL warrants further study, using a broader spectrum of genotyping and larger cohorts of patients.<sup>8</sup> From radiographic findings of cervical spine, thoracolumbar spine, and calcaneus, this patient was diagnosed as having OPLL and DISH.

Until now, there are no reports of the coexistence of CD, DISH, and OPLL. It is not clear whether the causes and pathology of these diseases are connected with each other directly. Dysregulated overproduction of IL-6 is responsible for the clinical abnormalities,<sup>15</sup> and is associated with osteoporosis.<sup>16</sup> The cardinal symptoms such as fatigue, high fever, and swollen glands in this case were reduced by corticosteroid therapy, and disease activity and the level of IL-6 were thought to be under control. However, it is possible to produce actual symptoms of ossifying/calcified diathesis of entheses and ligaments as a consequence, like the pathology of calcification found in the spleen. Moreover, compression fractures of the multiple thoracic vertebrae and osteoporosis had been observed. Disease activity in this case may be associated with compression fractures of the multiple thoracic vertebrae and osteoporosis.<sup>16</sup> Otherwise, recent data indicate that IL-6 could influence bone formation in conditions of increased bone turnover.<sup>17</sup> Therefore, we are of the opinion that those pathological situations of CD influenced the complicated bone turnover in this case.

This patient also suffered from polyarthralgia, and titer of the RAHA test was positive. However, radiographic find-



**Fig. 5.** Radiographic findings in the left knee joint showed the change like osteoarthritis, and the pathological findings of the synovial tissue showed little inflammatory change. A total knee arthroplasty was performed

ings showed the change as resembling osteoarthritis, and no abnormal change suggested rheumatoid arthritis (RA) in the bilateral hands and feet. Also, the pathological findings of the synovial tissue collected from the left knee joint showed little inflammatory change (Fig. 5). Therefore, RA was not diagnosed in this patient.

In conclusion, we have reported herein a CD patient with DISH and OPLL. The etiology of the pathology of this patient is not clear, and there is the possibility that unidentified causative factors may have contributed. Further reports of similar cases must be accumulated in order to fully elucidate the underlying pathogenesis of CD with ossification/calcification.

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