



INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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Prospective Study of the Association Between NAT2 Gene Haplotypes and Severe Adverse Events with Sulfasalazine Therapy in Patients with Rheumatoid Arthritis

To the Editor:

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by chronic inflammation of synovial tissue, resulting in destruction of multiple joints and eventually leading to severe disability. Treatment of RA with disease modifying antirheumatic drugs can prevent joint destruction^{1,2} and reduce mortality³, yet important adverse events are associated with the use of these agents. Tanaka, *et al*⁴ reported that the occurrence of adverse events with sulfasalazine (SSZ) therapy might be dependent upon genetic variations of the N-acetyltransferase 2 (NAT2) gene. Recently, Taniguchi, *et al*⁵ conducted a retrospective replication study of the association between NAT2 polymorphisms and adverse events with SSZ therapy. We examined the association between NAT2 genotypes and severe adverse events with SSZ therapy among patients with RA in a prospective study.

More than 5000 patients with RA have attended the outpatient clinic of the Institute of Rheumatology, Tokyo Women's Medical University. More than 99% of those patients are Japanese. All patients with RA met the 1987 American College of Rheumatology classification criteria⁶. Of these 5000 patients, 20%–30% were treated with SSZ. Between May 2006 and April 2007, 4 of the SSZ-treated patients, all Japanese, required hospitalization for severe adverse events and were admitted to Aoyama Hospital, Tokyo Women's Medical University.

Our previous study of genotypes at 4 single-nucleotide polymorphism (SNP) sites in the NAT2 gene enabled us to infer the haplotypes and diplotypes configurations for the majority of Japanese individuals⁷. These 4 SNP yield 6 haplotypes in the NAT2 gene in the Japanese population: NAT2*4, NAT2*5B, NAT2*5E, NAT2*6A, NAT2*7B, and NAT2*13. NAT2*4 is the wild-type haplotype; the remaining haplotypes are mutant types. A TaqMan kit (Applied Biosystems, Foster City, CA, USA) was used to determine genotypes at the 4 SNP sites by allelic discrimination chemistry. Genotypes were determined at the 4 SNP loci in the NAT2 gene. From the genotyping data, we inferred the diplotype configuration for each individual, using Penhaplo software^{8,9}.

Table 1. Clinical characteristics of 4 patients with RA who experienced severe adverse events with sulfasalazine therapy.

Patient	Sex/Age, yrs	Interval, days*	Adverse Events	Complication	NAT2 Gene Haplotype
1	F 31	4	Fever, rash	SLE	*5B/*7B
2	M 70	16	Pancytopenia	SLE	*6A/*6A
3	F 35	17	Pancytopenia	—	*6A/*13
4	F 28	10	Fever, SJS	—	*6A/*6A

* Interval between initiation of treatment and first observation of adverse event(s). SJS: Stevens-Johnson syndrome; SLE: systemic lupus erythematosus.

Table 1 shows clinical characteristics of the 4 patients who experienced severe adverse events with SSZ therapy (1 g daily). Fever, pancytopenia, and severe rash, including Stevens-Johnson syndrome, occurred. The interval between initiation of SSZ treatment and first observation of severe adverse events was 11.8 ± 6 days (mean \pm standard deviation). Although 2 of 4 cases were complicated with systemic lupus erythematosus, disease activity was low and deteriorated no further after administration of SSZ. DNA samples from the 4 patients were collected with the approval of ethical committees of Tokyo Women's Medical University. Genomic DNA analysis revealed that all 4 patients lacked the NAT2*4 haplotype. Although we did not investigate the background of the NAT2 gene in RA patients at our outpatient clinic in this study, 2 articles from our institution had already indicated that the frequency of the diplotype configuration without the NAT2*4 haplotype was only 5.6%–7.5% in Japanese patients with RA^{4,5}.

Adverse events resulting from SSZ seem to be rare among Caucasians. The discrepancy may be explained by the fact that the NAT2*5 haplotype is common among Caucasians¹⁰ but not among Asians. It is likely that the majority of the Caucasians who lack the NAT2*4 haplotype possess at least one NAT2*5 haplotype copy. NAT2*5 haplotype may code for a leaky enzyme, although further studies are required to prove this.

We found that all 4 patients who experienced severe adverse events when treated with SSZ had the diplotype configuration without the NAT2*4 haplotype. Our observations suggest that lack of the NAT2*4 haplotype is strongly linked to adverse events with SSZ therapy in Japanese patients with RA.

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Supported in part by a grant from the Ministry of Health, Labour, and Welfare of Japan.

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Progressive Multifocal Leukoencephalopathy in a Minimally Immunosuppressed Patient with Systemic Lupus Erythematosus Treated with Dapsone

To the Editor:

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal demyelinating disease due to reactivation of a latent infection with the papova-like polyomavirus JC (JCV)^{1,2}. Although cases have been reported in immunocompetent patients³, most patients are severely immunosuppressed⁴. Interest in this infection in rheumatic disease has recently increased due to the reports of PML occurring in 2 patients with systemic lupus erythematosus (SLE) treated with rituximab⁵. There have been 24 cases reported of PML occurring in patients with SLE, and the topic of PML in patients with rheumatic diseases has recently been reviewed⁶. We describe an additional patient with SLE who developed PML while being treated with low-dose prednisone, hydroxychloroquine (HCQ), and dapsone. To our knowledge, this is the first case of PML occurring in a patient treated with dapsone.

The patient was a 62-year-old Caucasian woman with a 25-year history of SLE manifested in the past by pericarditis, recalcitrant cutaneous manifestations, and anti-DNA antibodies and hypocomplementemia, without renal or central nervous system manifestations. She was treated with prednisone 60 mg daily at her presentation with pericarditis. She had no recurrences of pericarditis and subsequently has been treated with low-dose prednisone every other day, except for occasional increases to no more than 20 mg daily for not longer than 3 weeks' duration. She had been treated with HCQ for 15 years and had been taking 600 mg daily for the past 8 months. Five years ago, she had received thalidomide for 8 weeks for treatment of antimalarial-resistant subacute cutaneous disease, but she had never been treated with azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab, or other biologic agents. Three months prior to onset of symptoms of PML, dapsone 100 mg daily was added to her regimen of

prednisone 2.5 mg every other day and HCQ 600 mg daily. In April 2006, she experienced sudden onset of left arm and left side facial numbness, left side apraxia and bradykinesia, and hesitancy in her speech. A brain magnetic resonance image (MRI) showed a focal lesion in the white matter of the right parietal lobe that was hypointense on T1-weighted images and hyperintense on T2-weighted and FLAIR images, with surrounding edema and an area of enhancement with gadolinium, measuring 3 × 1 cm. A biopsy of the lesion revealed focal infarction, reactive changes, and histiocytosis. B and T cells were present in the perivascular areas. No neoplasm was found. HIV antibodies were negative. Cultures were negative for bacteria, fungi, and acid-fast bacilli, but she was treated empirically with vancomycin, metronidazole, and ceftriaxone. After discharge, JC virus infection was documented on the basis of the histologic findings on brain-biopsy tissue of large, round, dark nuclei with "ground-glass" appearance consistent with infected oligodendrocytes. These cells were immunohistochemically positive for papova virus and p53. Perivascular lymphocytic infiltration and a background of macrophages were present. Her SLE was felt to be well controlled, dapsone was discontinued, and antibiotics were changed to cidofovir. A repeat MRI 3 weeks after presentation showed progression of the parietal lesion with enhancement measuring 4.5 × 2.5 cm. After 3 months of treatment, she developed severe bilateral uveitis, and cidofovir was discontinued. She was then given levetiracetam prophylactically because of extensive brain damage evident on MRI. In July 2006, her MRI showed improvement, the area of enhancement decreasing in size to 4 × 2.4 cm. By December 2006, the area of enhancement had all but disappeared (2 mm). Her most recent MRI, in July 2007, showed no area of enhancement. Her SLE has remained quiescent to date and she is presently taking HCQ 400 mg daily and levetiracetam. Her neurological deficits have improved steadily with both physical and speech therapy, although she retains some residual left side apraxia. She has been able to return to work full-time.

PML is an often progressive and fatal demyelinating disease reported to occur in both immunosuppressed and immunocompetent patients. Clinically, it is manifested by motor weakness, sensory deficits, limb and gait ataxia, visual loss, cognitive impairment and mental deficits, personality changes, and dementia, correlating with lesions in the subcortical white matter and cortical myelin⁷. Neuroimaging by brain MRI shows areas of hypointensity or isointensity in the subcortical white matter on T1-weighted images that are hyperintense on T2-weighted and FLAIR imaging⁸⁻¹⁰. Typical lesions do not exhibit either mass effects or contrast enhancement. Occasionally, however, the lesions may show surrounding edema and enhancement with gadolinium. These unusual radiologic findings have been most often observed in AIDS patients treated with highly active antiviral therapy, and may be associated with a more favorable outcome than classic PML¹¹. This inflammatory variant of PML has recently been observed in patients without HIV infection¹². These more unusual radiographic findings were observed in our patient. While these findings are considered characteristic of so-called inflammatory PML, the diagnosis in our patient was established definitely by the pathological and immunohistochemical findings on brain biopsy, which are considered the gold standard. Pathologically, the JC virus infects the nuclei of oligodendrocytes and astrocytes and such nuclei are large, round, and dark with a glassy or "ground-glass" appearance. The JCV-infected cells can be confirmed by immunohistochemistry for polyomavirus proteins, as was the case with our patient, or *in situ* hybridization for JCV DNA on infected tissue^{13,14}. As an alternative to brain biopsy, the diagnosis of PML can be established by polymerase chain reaction detection of JCV DNA in cerebrospinal fluid (CSF)¹⁵.

With this additional patient, there are now 25 patients with SLE who have developed PML reported in the literature. This patient had not been treated with immunosuppressive medications for several years prior to the onset of her JCV infection, was not immunosuppressed at the time of JCV infection, and was HIV negative. A unique feature is that this appears to be the first reported patient to develop PML while taking dapsone. Dapsone is an antiparasitic agent most often used to treat leprosy, *Pneumocystis*

carinii, and dermatitis herpetiformis. It is useful in treating cutaneous vasculitis and cutaneous lupus^{16,17}. Dapsone has minimal effects on T and B cell mitogenesis¹⁸, and its mechanism of action appears to be related to its effects on neutrophil function and adherence¹⁹⁻²¹. Its use in SLE is based on its utility in other cutaneous diseases and favorable clinical responses in patients with cutaneous lupus, although its specific mechanism of action in systemic lupus has not been elucidated. PML has been reported to occur in patients treated with natalizumab, an antagonist of $\alpha 4$ integrin, a biologic agent used in patients with multiple sclerosis and Crohn's disease, with planned uses in rheumatoid arthritis^{22,23}. It has been hypothesized that natalizumab may promote the development of PML, at least partially by its blockade of trafficking of hematologic cells into the CSF^{24,25}. It is possible that dapsone, by its inhibition of neutrophil function and adherence, could in a similar manner disrupt inflammatory cell trafficking into the CSF. However, until further cases of PML occur in patients taking dapsone, the present case must be considered a coincidental occurrence.

Several years before the onset of JCV infection, the patient was treated with thalidomide. Thalidomide is a known inhibitor of proinflammatory Th1 cytokines, most notably tumor necrosis factor- α ²⁶. However, she had not taken this medication in many years and it is unlikely that it had any longterm effects on her level of immunocompetency. Aside from the use of dapsone, she was not receiving immunosuppressive agents in the conventional sense. She therefore is the tenth of the reported 25 SLE patients with PML to be relatively immunocompetent at the time of JCV infection. This suggests that factors other than iatrogenic immunosuppression, including SLE itself, may be contributing to susceptibility to JCV infection in these patients.

Despite the short duration of treatment with cidofovir, limited by the development of drug-induced uveitis²⁷, this patient has improved steadily. As noted in the literature, gadolinium enhancement of the parietal lesion on MRI scanning, consistent with inflammatory PML, and its subsequent resolution coinciding with her clinical improvement, may have favorable prognostic significance^{11,12}. It is possible that the relative immunocompetency of this patient contributed to her positive outcome.

In summary, this is a case of a minimally immunosuppressed patient with SLE who developed PML while taking dapsone, a medication not previously associated with development of PML. Although dapsone has effects on leukocyte trafficking that could affect susceptibility to JCV infection, this association must be considered coincidental until further cases are reported. While profound immunosuppression is the usual background in non-lupus patients with PML, 40% of the reported patients with SLE have been relatively immunocompetent at the time of JCV infection. Our patient's relative immunocompetence may have contributed to her positive outcome.

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Pseudotumoral Presentation of Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

To the Editor:

Chondrocalcinosis is a microcrystalline disease characterized radiographically by multiple foci of calcification in hyaline and fibrocartilage of the joints and intervertebral discs. Initially described by Zitnan and Sit'aj¹, it has recently been more appropriately designated calcium pyrophosphate dihydrate (CPPD) crystal deposition disease. This term also encompasses the tumorous form of the disease, designated tophaceous pseudogout.

We describe 2 cases of tophaceous pseudogout presenting as a single calcified soft-tissue mass with no evidence of CPPD crystal deposition disease in any other joint.

Case 1. A 76-year-old woman presented with a history of swelling and increasing pain of the right popliteal fossa leading to inability to bend the knee. In her history, she mentioned asthma in childhood and a Colles fracture 2 years before presentation. On examination, the overlying skin was normal. Palpation revealed a soft-tissue mass in the popliteal fossa associated with moderate pain. Laboratory findings were normal; in particular there was no inflammatory syndrome. Conventional radiographs and multidetector computed tomography (MDCT) showed a 3-cm nodular mass in the popliteal fossa, with multiple central or peripheral, arciform and annular calcific deposits suggesting a cartilaginous matrix. The mass was responsible for a large erosion of the adjacent bone, i.e., the posterior cortex of the femoral metaphysis. Considering the cartilaginous characteristics of the tumoral matrix and the presence of pain, which could not be explained by any associated intraarticular disorder, the diagnosis of subperiosteal chondrosarcoma was suspected and a surgical ablation of the tumor was performed.

Histopathologic analysis showed deposits of CPPD crystals bordered by a fibrous connective tissue presenting a lobulated pattern with areas of chondroid metaplasia. The crystals were short, rod-like to rhomboid, and birefringent under polarized light. A diagnosis of tumorous calcific collection with CPPD crystal deposition was made, also designated tophaceous pseudogout (Figure 1). Conventional joints including wrists, knees, and pubic symphysis were radiographed after the diagnosis to look for typical signs of intraarticular CPPD disease. Radiographs showed no calcific deposits on the hyaline or fibrocartilage.

Case 2. A 41-year-old woman complained of gradually increasing pain of the hip for several years. She reported a major ski accident in the past (6 years previously) with a large hematoma of the anterior proximal portion of the thigh. She had no relevant medical or surgical history. Conventional radiographs, ultrasound, and high resolution MDCT showed a widely calcified and well circumscribed 4-cm mass of the iliopsoas tendon. The characteristics were those of a benign highly calcified lesion resembling a tumoral calcinosis. On magnetic resonance imaging (MRI), the lesion showed low signal intensity on T1-weighted images and high signal intensity on T2-weighted sequences with gadolinium enhancement. These MRI patterns are also those of the cartilaginous lesions. Because of recurrent pain and a slow increase of the size of the lesion, surgical ablation was performed.

Histopathologic and microscopic examination showed a calcified



Figure 1. Case 1. Sagittal CT section shows well defined soft-tissue mass with arciform and annular calcification.

tumor with a fibrous stroma and broad areas of crystalline deposits associated with focal spots of chondroid metaplasia and giant cells. The crystals were rhomboid and birefringent under a polarized light. The diagnosis proposed was CPPD crystal deposition disease. Typically involved joints were screened to look for articular CPPD deposition.

Three years later, a soft-tissue mass developed in the hip again, with features similar to the previous episode. Needle biopsies and steroid infiltration were performed under MDCT control. Microscopic examination found similar patterns to those of 3 years before, and the diagnosis of pyrophosphate tophus recurrence was confirmed (Figures 2 and 3). She returned 6 months later with increasing pain of the same thigh and then underwent surgery. Complete ablation of the tumor was performed and the diagnosis of pyrophosphate tophus recurrence was confirmed.

CPPD disease is characterized by the presence of crystal deposits in hyaline and fibrocartilage of the joints. CPPD crystal deposition disease is generally observed in middle-aged and elderly patients. Initial descriptions emphasized the occurrence of "pseudogout" attacks, but further investigations revealed multiple additional clinical patterns. These patterns emphasize the capacity of the disease to mimic a variety of other conditions including gout, rheumatoid arthritis, degenerative joint disease, neuropathic osteoarthropathy, and a rare condition described here, tophaceous pseudogout.

Soft-tissue calcified mass (tophaceous pseudogout) is a rare presentation of CPPD disease, as described²⁻⁹. Some reports³⁻⁶ describe highly calcified masses that are difficult to differentiate from tumoral calcinosis. Some others emphasized radiological similarities with benign or malignant cartilaginous lesions.

Our cases support these various data, as initial diagnosis was tumoral calcinosis in one case and subperiosteal chondrosarcoma in the other. Differentiation between the latter condition and pseudogout is difficult because of the presence of arciform and annular calcifications within the soft-tissue mass. Diagnosis can be made even more difficult by histological data that can show areas of chondroid metaplasia, sometimes associated with cellular atypia, simulating once again a cartilaginous lesion^{4,10}. Surgical ablation is therefore necessary to identify the CPPD crystals in the mass, in order to avoid misdiagnosis of benign or malignant cartilaginous lesion. In both our cases, metaplastic areas of cartilage were seen, but with no cellular atypia. In most reports, the soft-tissue masses were associated with calcifications within hyaline or fibrocartilage, making the diagnosis relatively easy. Lambrecht, *et al*¹⁰ reported the case of a well circumscribed mass of amorphous calcification located in the soft tissue adjacent to the lesser trochanter. In that case, calcific deposits were present in the symphysis pubis and the femoral head. In another case⁵ the tophaceous pseudogout of the sternoclavicular joint was also associated with severe pluriarticular chondrocalcinosis. Maugars, *et al*¹¹ reported large periarticular calcifications of the hips and pubis in a woman with diffuse primary chondrocalcinosis, symptomatic in the knees. Serial articular and periarticular biopsies



Figure 2. Case 2. MDCT axial native section shows a widely calcified mass in the psoas tendon. There is no intraarticular disorder.

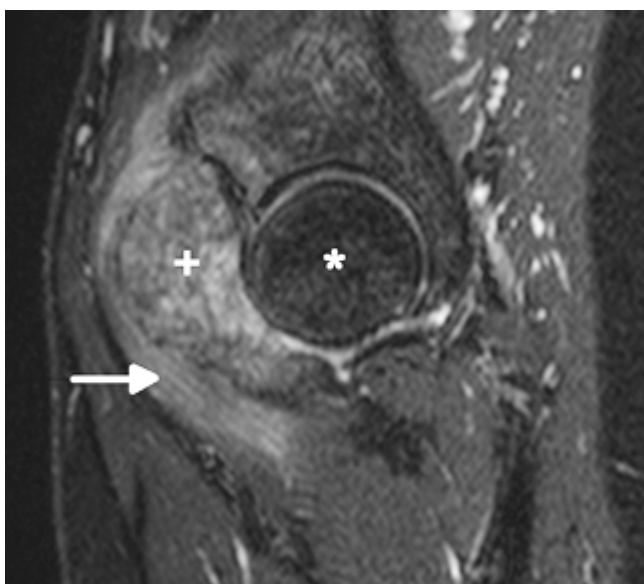


Figure 3. Case 2. Sagittal T2 fat-suppressed MR image taken simultaneously with that in Figure 2. There is edema within and adjacent to the lesion (+) involving the psoas muscle (arrow). The femoral head remains normal (*).

showed CPPD in cartilage, synovia, capsula, tendon, and muscle. In contrast, in both our cases, no calcific deposits were found in other joints, making the diagnosis almost impossible as long as the typical radiological patterns were not present. This specific pattern makes us question the most appropriate term to designate this disease.

Based on literature data, the locations most commonly involved with tophaceous pseudogout are the wrist and digits^{2,3,9}, the infratemporal fossa, and the temporomandibular joint^{4,7,8,12}. However, many other locations can be involved, such as the para-ischial region¹⁰, the base of the neck, cervical spine^{6,13}, sternoclavicular joint⁵, and mitral valve¹⁴.

To our knowledge, our report is the first to describe CPPD disease involving the iliopsoas tendon. Lambrecht, *et al*¹⁰ described tophaceous pseudogout adjacent to the lesser trochanter, but the lesion was intimately

associated with the semimembranous tendon. Sissons, *et al*⁹ also reported the presence of a highly cellular lesion adjacent to the right hip. The mass was located in the tissues adjacent to the bone and contained deposits of CPPD crystals.

Surgical ablation of these lesions is the rule, mainly because this diagnosis is usually not established and histopathologic confirmation is needed. Complete ablation is required, because the lesion is at risk of recurrence after partial and sometimes even complete ablation^{15,16}. We observed a recurrence in one of our cases, after complete excision of the mass located in the iliopsoas myotendinous junction. Three years after surgery, a 3.5-cm mass reappeared at exactly the same location.

Because of its unusual presentation, location, and histology, tumoral CPPD crystal deposition presenting as a single soft-tissue calcified tumor may be misinterpreted as a soft-tissue cartilaginous lesion or tumoral calcinosis. It is necessary to identify the CPPD crystal components on biopsy fragments to avoid misdiagnosis.

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Corrections

Song I-H, Appel H, Haibel H, et al. New onset of Crohn's disease during treatment of active ankylosing spondylitis with etanercept. *J Rheumatol* 2008;3:532-6.

In the note "Added in Proof" to this report, the number "10" represents reference 10, and should appear in superscript, as follows. We regret the error.

"Added in Proof. During preparation of this manuscript, a fourth case of new onset of Crohn's disease during etanercept therapy was observed in our department; a 34-year-old male patient with AS who also participated in the clinical trial¹⁰ developed new onset of CD 66 months after initiation of etanercept."

Qazi U, Lam C, Karumanchi SA, Petri M. Soluble Fms-like tyrosine kinase associated with preeclampsia in pregnancy in systemic lupus erythematosus. *J Rheumatol* 2008; 35:631-4. A disclosure statement should have been published with this report, as follows: Dr. Karumanchi is a co-inventor on multiple patents filed by Beth Israel Deaconess Medical Center for the diagnosis and therapy of preeclampsia. He is a consultant to Beckman Coulter, Abbott Diagnostics, and Johnson & Johnson. We regret the error.