A Japanese case of familial Mediterranean fever presenting diffuse bone marrow uptake of FDG-PET and high levels of neutrophil membrane CD64 expression

Siix, FMF is a rare inflammatory disease characterized by recurrent attacks of fever and inflammation. Even though some useful diagnostic criteria have been proposed, useful imaging methods or haematological markers for the diagnosis or follow-up of FMF have not been established. We experienced a case of a 46-year-old woman with FMF presenting diffuse bone marrow uptake of $^{18}$F fluoro-deoxy glucose (FDG) and high levels of polymorphonuclear neutrophil (PMN) membrane CD64 expression.

A 46-year-old Japanese female was admitted to our hospital because of chest pain and fever of undetermined origin (FUO). She had been suffering from a periodic fever since she was 18-years old. $^{18}$F FDG-PET was performed, revealing diffuse bone marrow uptake of $^{18}$F FDG (Fig. 1). In the laboratory findings of haematology and biochemistry at the time of admission, there were no abnormalities except for elevated ESR and elevated levels of CRP (ESR 51 mm/h, CRP 6.54 mg/dl). Tests for ANAs, ANCAs and RF were negative. A peripheral blood smear revealed no abnormalities. Serum M-protein was not detected by immunofixation. Since we suspected FMF based on these findings, we performed the sequencing of all 10 exons of the ME芙 gene and detected a heterozygous mutation (GAG to AAG) in codon 84 of exon 1 of the ME芙 gene that resulted in a substitution of lysine for glutamic acid (E84K). In light of these findings, we initiated daily colchicine treatment (1.0 mg/day), and the patient’s clinical manifestation rapidly improved. FMF was diagnosed according to clinical criteria for the diagnosis in combination with a classification tree format [1].

The expression of CD64 on PMNs in healthy subjects, before and after treatment, was measured by flow cytometry using a Coulter Epics XL flow cytometer (Beckman Coulter, Brea, CA, USA) using Expo32 ADC analysis software (Beckman Coulter). Before the colchicine treatment, the patient’s mean fluorescence intensity (MFI) of CD64 on PMNs was significantly increased (MFI: 12.4) compared with those of healthy subjects (MFI: 7.4). Colchicine treatment (1.0 mg/day) down-regulated the increased CD64 expression, but expression was higher than in healthy subjects (MFI: 7.4).

FMF is prevalent among populations surrounding the Mediterranean Sea. However, more cases have been reported in countries not related to this area, including Japan. In countries where FMF is rare, a clinical diagnosis of FMF may not be easy, and the role of genetic testing is crucial. More recently, Tomiyama et al. [2] reported a new ME芙 mutation, E84K, in a Japanese FMF patient.

Hyperfunction of PMNs is a characteristic of FMF. CD64 (FcR1), a factor crystallizable (Fc) receptor for immunoglobulin G (IgG), plays a role in antibody-dependent cytotoxicity, clearance of ICs and phagocytosis of targets.

References


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opsonized with IgG. The utility of CD64 (FCgR1) expressed on PMNs in clinical situations has been investigated. Matsui et al. [3] demonstrated that quantitative measurement of CD64 expression on PMNs can be used as a sensitive and specific marker to detect infection complicating RA. More recently, S100A12, a product of activated neutrophils, has been demonstrated to be a sensitive biomarker for FMF [4]. It is likely that the CD64 expression of neutrophils has great clinical utility in the formulation of a differential diagnosis for FMF, since the hallmark of FMF is PMN activation. In the present case, we demonstrated that CD64 expression on PMNs was elevated in FMF patients compared with healthy subjects, suggesting that PMN CD64 expression is an ideally responsive diagnostic indicator of FMF.

Recently, many studies have shown that the administration of G-CSF can cause homogeneous hypermetabolic activity of bone marrow in PET using [18F]FDG [5–7]. Since G-CSF stimulates PMNs, G-CSF-induced uptake of [18F]FDG may be related to the increased activity of PMNs in bone marrow. A similar phenomenon might occur in patients with FMF, as shown in this case. Although our experience is limited to one patient, we suggest that both [18F]FDG-PET uptake in bone marrow and CD64 expression on PMNs reflect the activation of PMNs in patients with FMF and could be novel tools for the diagnosis of FMF.

**Rheumatology key message**

- FDG-PET and CD64 on PMNs are useful for diagnosis of FMF.

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First report of anti-calcium-sensing receptor antibodies in a patient with Sjögren’s syndrome and primary hypoparathyroidism

Sr, SS is a multisystem autoimmune disease that chiefly affects salivary and lacrimal gland function. The disease is characterized by lymphocytic infiltration of the exocrine glands, resulting in oral and ocular dryness, and the presence of anti-La and anti-Ro antibodies (Abs) [1]. Frequently, SS is associated with other autoimmune diseases including autoimmune hypothyroidism and Graves’ disease [2–5]. In 1979, a patient with RA and dry eyes was reported to have hypoparathyroidism, but this was not proved to have an autoimmune origin [6]. Previous studies have demonstrated that hypoparathyroidism can have an autoimmune pathogenesis due to immune responses that either destroy the parathyroid or that give rise to Abs that aberrantly stimulate the calcium-sensing receptor (CaSR) on parathyroid gland chief cells [7–9]. The aim of the current study was to investigate the cause of hypoparathyroidism in a patient with SS in order to determine whether an autoimmune aetiology was possible.

A 45-year-old female who satisfied 2002 criteria for SS was first found to be hypocalcaemic in 2001 with a corrected total serum calcium concentration of 2.04 mmol/l (normal range 2.15–2.65 mmol/l). The 25-hydroxyvitamin D level was <15 nmol/l (normal range 50–140 nmol/l) and calcium and vitamin D supplementation were given leading to normalization of 25-hydroxyvitamin D to 98 nmol/l. Serum magnesium, phosphate and alkaline phosphatase levels were normal. Hypocalcaemia fluctuating between 2.03 and 2.10 mmol/l persisted while 25-hydroxyvitamin D levels increased to 125 nmol/l. In 2009, serum PTH was undetectable at <10 ng/l (normal range 8–55 ng/l) paired with a low corrected serum calcium, a finding reproduced in a subsequent sample. The patient had a right-sided parotidectomy in 1995 revealing a lymphoepithelial lesion consistent with Mikulicz’s syndrome. There had been no surgeries on her thyroid or parathyroid gland. Physical examination showed no features of other autoimmune conditions.

A diagnosis of primary hypoparathyroidism in this patient with SS was made when low serum calcium levels were found in the presence of a low level of PTH. The patient’s normal renal function excluded the possibility of hypocalcaemia caused by renal disease and there was no evidence of intestinal dysfunction. Normal magnesium levels discounted this as a possible cause of insufficient PTH secretion. Serum calcium levels had remained normal for at least 4 years after parotidectomy increasing assurance that the parathyroid glands had been untouched. It is unlikely that hypoparathyroidism resulted from abnormally developed parathyroid glands or CaSR-activating mutations that reduce PTH secretion, as calcium levels were normal before 2000 and there was no suggestive family history. At least 30% of SS patients suffer from at least one additional autoimmune condition, most commonly hypothyroidism [2–5]. An autoimmune pathogenesis for this patient’s hypoparathyroidism was therefore investigated by evaluating for the presence of anti-CaSR Abs [7–10].

Anti-CaSR Abs were measured in the patient’s serum in a specific immunoprecipitation assay as previously described [10]. The patient was positive for anti-CaSR Abs with a CaSR Ab index of 21.6 (normal range, CaSR Ab index 0.15–1.72) (Fig. 1A). The effects of the patient’s anti-CaSR Abs on CaSR function were determined using HEK293 cells expressing the CaSR (HEK293-CaSR cells). Cells were incubated with immunoglobulin G (IgG) before measurement of Ca2+-induced, CaSR-mediated inositol-1-phosphate (IP1) accumulation and extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation [8]. The results indicated that the patient’s IgG did not significantly affect the levels of either IP1 accumulation or ERK1/2 phosphorylation in HEK293-CaSR cells when responding to Ca2+ (Fig. 1B and C).

The main function of the CaSR is to regulate calcium balance by sensing changes in serum calcium concentration [11]. Anti-CaSR Abs have been shown to activate the CaSR leading to low levels of PTH secretion in patients with isolated autoimmune hypoparathyroidism and in the context of autoimmune polyendocrine syndrome type 1 [8–10]. The anti-CaSR Abs detected in this patient’s serum did not appear to activate the CaSR. This may reflect low Ab levels that fail to stimulate the receptor in the functional assays used or non-activating anti-CaSR Abs that cause damage through complement fixation [7].

Hypoparathyroidism has only been reported in one previous case of SS that may not have satisfied 2002 criteria and in which an autoimmune pathogenesis for hypoparathyroidism was not proved [1, 6]. Our report, therefore, details the first case in which anti-CaSR Abs have been detected in a patient with SS and primary hypoparathyroidism. Ab-mediated salivary gland destruction has been demonstrated in an animal model of SS [12]. This patient’s low PTH levels might have resulted from autoimmune parathyroid destruction that reflects the underlying pathogenic mechanism of SS [12]. Alternatively, an analogy can