that aberrantly stimulate the calcium-sensing receptor that either destroy the parathyroid or that give rise to Abs have demonstrated that hypoparathyroidism can have an autoimmune origin [6]. Previous studies reported to have hypoparathyroidism, but this was not disease [2].

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 diagnosed 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 levels were normal. Hypocalcaemia fluctuating between 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
Fig. 1 (A) Detection of anti-CaSR Abs in the SS patient’s serum. Sera from the patient and 20 healthy subjects were evaluated for anti-CaSR Abs in a specific immunoprecipitation assay at 1:20–1:1000 dilutions, as described previously [10]. The CaSR Ab indices are shown for the patient’s serum samples at each dilution and are the mean of three experiments. The patient was positive for anti-CaSR Abs with a CaSR Ab index of 21.6 at a 1:20 serum dilution and anti-CaSR Abs were detectable up to a serum dilution of 1:200. The mean (s.d.) CaSR Ab index is also shown for the 20 healthy control sera assayed at a 1:50 dilution. (B and C) Effect of the SS patient’s IgG on the response of the CaSR-mediated stimulation of HEK293-CaSR cells by Ca^{2+}. Changes in IP1 accumulation and ERK1/2 phosphorylation levels were measured in response to Ca^{2+} at 0, 0.5, 1.5, 3.0 and 5.0 mmol/l in HEK293-CaSR cells pre-incubated with the patient’s IgG sample at a 1:50 dilution [8]. IgG samples from six healthy subjects and from an individual with anti-CaSR-activating Abs (positive control) were also tested [8]. HEK293-CaSR cells without pre-incubation with IgG were included. The results of three experiments show: (B) IP1 accumulation and (C) ERK1/2 phosphorylation, in Ca^{2+}-stimulated HEK293-CaSR cells pre-incubated with IgG from either the patient, a single healthy subject or the positive control, or that were not pre-incubated with IgG. The patient’s IgG did not significantly affect the levels of either IP1 accumulation or ERK1/2 phosphorylation: P-values were >0.05 in t tests when comparing HEK293-CaSR cells pre-incubated with the patient’s IgG, control IgG and without any pre-incubation.
be drawn with Hashimoto’s thyroiditis in which almost all patients have thyroid peroxidase Abs, but the initiation of thyroid destruction is believed to be T-cell mediated. In conclusion, clinicians should be aware of a possible autoimmune cause for hypoparathyroidism in patients with SS.

**Rheumatology key message**
- CaSR Abs may define hypoparathyroidism in SS.

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References


Anti-synthetase syndrome positive for anti-isoleucyl-tRNA synthetase antibodies: an unusual case overlapping with systemic sclerosis and Sjögren’s syndrome

Sir, Anti-synthetase syndrome (ASS) is characterized by inflammatory myositis associated with interstitial lung disease and anti-synthetase antibodies [1]. Other symptoms, including arthritis, RP and mechanic’s hands also belong to ASS [2]. Several anti-synthetase antibodies have been described; anti-Jo1 being the most common. Very little is known about the clinical manifestations of the ASS associated with anti-isoleucyl-tRNA synthetase antibodies (anti-OJ antibodies), most likely because anti-OJ antibodies are particularly rare (<3% of myositis) and have not been routinely investigated in the past. Only 18 patients have been reported in the English literature [3–6]. We report an unusual patient with anti-OJ-positive ASS overlapping with SSC and SS.

A 21-year-old African woman was admitted with digital ulcers. She complained of recent RP, gastro-oesophageal reflux, brief arthralgia and dry eyes. Clinical examination and chest X-ray were normal. However, over the next 2 months, she developed a progressive dyspnoea associated with muscle weakness (graded as 3+/5 by manual muscle test). Pulmonary examination revealed fine crackles. A high-resolution chest (CT) scan showed diffuse interstitial pneumonia, with a predominant honeycomb pattern (usual interstitial pneumonia) and pulmonary function tests revealed a restrictive syndrome [vital capacity (VC) = 26%] and carbon monoxide transfer factor (TLCO) was dramatically decreased (26%). Muscular investigations confirmed severe myositis: creatine phosphokinase = 11 700 IU/l (normal range <160 IU/l) and electromyography showed a myogenic syndrome. Muscle biopsy showed endomysial infiltrates with a majority of B cells without vasculitis; immunohistochemistry also showed diffuse MHC class I over-expression, but was negative for complement terminal membrane attack.