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CASE REPORT

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Gustatory sweating due to autonomic neuropathy in a patient with amyloidosis secondary to rheumatoid arthritis

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Abstract Autonomic neuropathy, although often reported to occur in patients with AL (amyloid of light chain of immunoglobulin) amyloidosis, is extremely rare in AA (amyloid A) amyloidosis. We describe a patient with AA amyloidosis secondary to rheumatoid arthritis (RA) in whom autonomic neuropathy resulted in gustatory sweating during the end stage of RA. We discuss the importance of gustatory sweating as a characteristic sign of autonomic nervous system dysfunction in AA amyloidosis secondary to RA, and stress the availability of cardiovascular autonomic tests as an indicator of autonomic neuropathy in not only AL amyloidosis but also AA amyloidosis.

Key words Amyloidosis · Dysautonomia · Gustatory sweating · Rheumatoid arthritis (RA)

Introduction

Secondary amyloid A (AA) amyloidosis is an uncommon yet important complication of rheumatoid arthritis (RA). AA amyloidosis secondary to RA is a serious and potentially life-threatening disorder caused by the tissue deposition of insoluble fibrillar proteins, termed AA, derived from high circulating concentrations of the acute-phase precursor protein serum amyloid protein A (SAA). Proteinuria is the most common presenting manifestation of amyloidosis, although renal failure, gastrointestinal hemorrhage, malabsorption, hepatosplenomegaly, cardiac involvement, bladder hemorrhage, or peripheral neuropathy may occur during the course of the illness.[1,2]

Autonomic neuropathy occurs in approximately 15% of patients with AL (amyloid of light chain of immunoglobulin) amyloidosis;[3] however, this complication is extremely rare[1,4] in AA amyloidosis compared with other complications mentioned above. Dysautonomia has been previously reported in only a few patients who had amyloidosis secondary to chronic diseases, such as RA, tuberculosis, and glomerulonephritis.[5] The association of gustatory sweating with diabetes mellitus has been linked to autonomic nervous system involvement.[6,7] We present a case of AA amyloidosis secondary to RA in whom symptoms of gustatory sweating due to autonomic neuropathy dominated the terminal stage of the illness.

Case report

A 74-year-old woman who was born in Kumamoto, Japan, where there is a genetically high risk of familial amyloidotic polyneuropathy (FAP), had neither congenital base nor family history of FAP, and had been suffering from RA with both polyarthralgia and morning stiffness since the age of 58 years. She had been treated with nonsteroidal anti-inflammatory drugs, long-term and aggressive disease-modifying antirheumatic drug (DMARD) therapy, and prednisolone, but had uncontrolled active inflammation in multiple joints, with resulting articular functional disability. Right total elbow joint arthroplasty and right total hip joint arthroplasty were performed in 1997. She complained of severe nuchal pain from rheumatoid involvement in the cervical spine, and X-rays showed atolantoaxial subluxation. Magnetic resonance imaging showed rheumatoid cervical spondylitis with malalignment of the cervical spine, but neither cervical cord compression nor cord damage. In June 2000 she developed anorexia, frequent diarrhea, and

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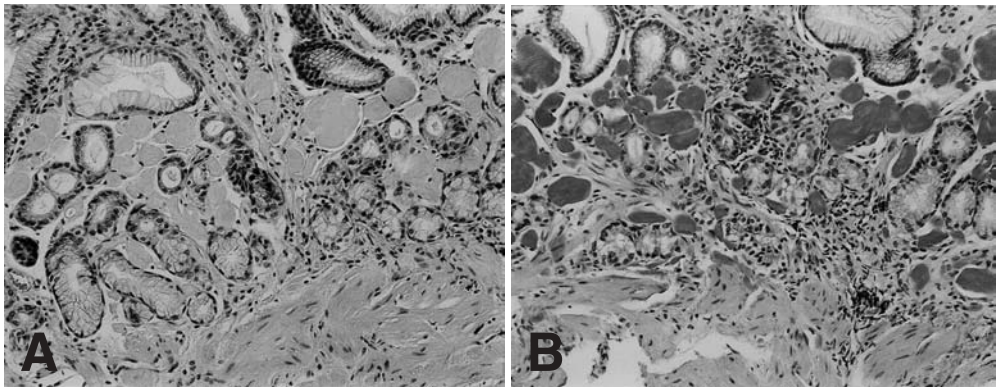

Fig. 1A,B. Microscopic findings of biopsied gastric mucosa. **A** Gastric biopsy showing multiple diffuse nonstructural substances which were eosinophilic on hematoxylin–eosin staining in the submucosal layer (×150). **B** Amorphous substances seen in **A** were remarkably positive for Congo-red staining revealed as amyloid deposition (×150)

weight loss (3 kg in 3 months), and was transferred to our center. Physical examination revealed an alert, oriented female in no acute distress and without evidence of Sjögren's syndrome. Blood pressure was 128/62 mmHg, and her pulse was regular at 84 beats/min. Her erythrocyte sedimentation rate was 68 mm/h (normal 3–15), C-reactive protein 5.9 mg/dl (<0.5), SAA 287 μg/ml (<8), and rheumatoid factor 293 U/ml (<35). No other autoantibodies were detected, and serum complement (CH_{50}) was 29 U/ml (normal 30–45). Proteinuria was 3(+). Occult blood tests were positive in both the urine and stool. Her serum creatinine level was 0.9 mg/dl (0.6–1.5), blood urea nitrogen 22 mg/dl (5–20), urate 5.7 mg/dl (2.3–5.7), aspartate aminotransferase 46 IU/l (5–40), alanine aminotransferase 51 IU/l (<35), and lactate dehydrogenase 468 IU/l (100–500). Immunoelectrophoresis of both serum and urine protein showed normal patterns, which suggested absence of neoplasms involving plasma cells or lymphocytes. Hemoglobin A_1C was 5.3% (<6.0), fasting blood sugar was 89 mg/dl (70–100), and glucosuria was absent. Thyroid hormone levels were within the normal limits. Low R-wave voltage on the electrocardiogram (ECG), an increased cardiothoracic ratio on the chest roentgenogram, and granular sparkling of the left ventricular wall on echocardiography were all suggestive of cardiac dysfunction. An upper gastrointestinal series showed chronic gastritis, and biopsy of the gastric mucosa revealed amyloid deposition (Fig. 1). This specimen was positive for Congo-red staining, that was susceptible to oxidative treatment with potassium permanganate. Green birefringence on polarization microscopy after Congo-red staining of the specimen was recognized. A renal biopsy was requested to examine whether renal amyloid deposition existed, but the patient did not accede. Based on these findings, we diagnosed the patient to have secondary amyloidosis associated with RA. Furthermore, the polymerase chain reaction-based restriction fragment length polymorphism assay[8] revealed that her SAA1 genotype was a SAA1.1/1.3 heterozygote, in which the SAA 1.3 allele is strongly suggested to be a risk factor for Japanese AA amyloidosis secondary to RA.[9]

During the course of her admission the patient began to complain of diffuse facial sweating, more prominent on her left cheek. It occurred whenever, and with whatever, she ate. The sweating would begin on her left forehead and scalp, then involve the left side of her face, and extend to the base of her neck, where it would stop abruptly at the level of the third cervical dermatome. Below this level there were only small, isolated patches of sweat production, with large areas of anhydrosis. Photographs were taken but did not clearly capture the findings, because an indicator such as the Minor iodine starch test was not applicable. The diaphoresis lasted for 5–10 min after cessation of eating. Environmental temperature did not appear to alter these symptoms, and these episodes had nothing to do with hypoglycemia. At the same time, she also complained of dizziness, a symptom which became severe and which was associated with profound postural hypotension (137/86 mmHg supine, 94/65 mmHg sitting, 62/34 mmHg standing). Horner's syndrome-like symptoms (miosis and blepharoptosis) were sometimes recognized in her left eye, but were not always significant. Neurogenic muscle weakness, peripheral signs of mononeuritis multiplex and/or multineuritis, and numbness of extremities were not noted during her clinical course, so there was no evidence of peripheral sensorimotor neuropathy. Changes of heart rate related to postural position were recorded by ECG (Fig. 2). After the patient rested in the supine position for at least 15 min, the coefficient of variation (CV) was calculated from the mean values (MV) and standard deviations (SD) from 100 sequential R-R intervals on the ECG using the following formula; CV (%) = SD/MV × 100. At rest, CV was 1.22 and, after deep breathing for 1 min, CV was 1.45. The ratio was also obtained from the 15th and 30th R-R interval after standing from the supine position, and the 30:15 ratio was 0.94. The patient performed a Valsalva maneuver by blowing with an expiratory pressure of 40 mmHg for 10 s into a mouthpiece attached to a mercury manometer. The Valsalva ratio (ratio of the longest R-R interval recorded after the Valsalva maneuver to the shortest one recorded during the maneuver) was 1.04. Autonomic dysfunction suggested by signs and symptoms was further confirmed with cardiovascular autonomic tests. The summary of these results is shown in Table 1. We concluded that gustatory sweating in this case was attributable to AA amyloidosis secondary to RA.

Gustatory sweating continued to be a concern to the patient, and she requested therapy. Considering the multiple comorbid conditions and the patient's age, systemic

Table 1. Summary of cardiovascular autonomic tests

	Present case	Normal values[a]
CV		
Resting	1.22 (%)	<2.48
Deep breathing	1.45 (%)	<1.10
30:15 ratio	0.94	≧1.00
Valsalva ratio	1.04	≧1.45
Postural hypotension (mmHg)		
Supine	137/86	
Sitting	94/65	
Standing	62/34	

CV, coefficient of variation
[a] Normal values from Refs. 1, 11, and 12 were employed

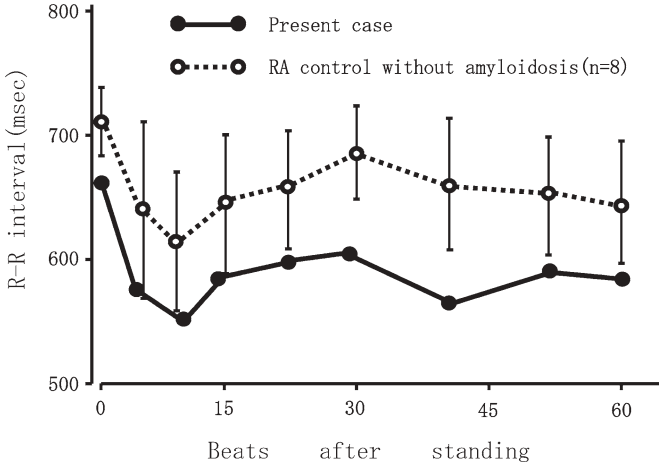

Fig. 2. Changes of R-R intervals after standing. The heart-rate response to standing of the present case (*closed circles*) compared with the rheumatoid arthritis (*RA*) control without amyloidosis (*open circles*) ($n = 8$) representing mean R-R intervals in the first 60 beats, denoted by mean ± SD. Generally, after standing, first tachycardia and subsequent relative bradycardia are characteristic in healthy subjects. In RA controls without amyloidosis, the response was less pronounced, as shown. The present case showed the least pronounced tachycardia-bradycardia response

anticholinergic agents were undesirable. In view of a report that diabetic gustatory sweating was responsive to botulinum toxin type A,[10] she was offered an intracutaneous injection of that medicine into the affected skin area as the treatment. However, she declined this option so the efficacy of that modality could not be assessed.

Discussion

Among the cases of nervous system involvement in RA, those of the peripheral nervous system are well documented, especially rheumatoid mononeuritis multiplex.[11] It is suggested that autonomic neuropathy in RA could relate to rheumatoid inflammatory activity and perhaps to peripheral nervous system involvement. Cardiovascular tests that are reliable, noninvasive, and easy to reproduce, explore the cardiac autonomic system, particularly parasympathetic and to a lesser extent sympathetic activity.[4] The present case demonstrated several manifestations that are typical of AA amyloidosis secondary to RA and of dysautonomia, which is very rare. The development of amyloidosis in a patient with persistently active and aggressive rheumatoid inflammation, and the occurrence of nephrotic involvement as its initial manifestation, are characteristic of RA. It is known that in various autonomic dysfunctions, peripheral autonomic nerves are first impaired prior to the sensory and motor nerves in FAP.[12] The occurrence of severe autonomic neuropathy, however, is extremely rare. Although autonomic neuropathy has been described in RA in the absence of amyloidosis,[3] these patients usually have only mild clinical manifestations of their autonomic neuropathy.[13] Other recognized causes of autonomic neuropathy, such as vasculitis, diabetes, uremia, or DMARD-induced, were not present in our patient. The abnormal postural hypotension was consistent with involvement of the autonomic nervous system. Both abnormal Valsalva and 30:15 ratios suggested that cardiac vagal function was also impaired (Table 1). Although it is not possible to prove beyond all doubt that amyloidosis caused the patient's autonomic neuropathy, the absence of other recognized causes, the progressive course in the setting of histologically proven amyloidosis, and the extensive symptoms and signs consistent with amyloidosis suggest that amyloidosis is causally related to the development of both autonomic neuropathy and associated gustatory sweating in the present case. Detection of amyloid deposition in gastric mucosa (Fig. 1) and signs and symptoms of defective cardiovascular function (Fig. 2 and Table 1) are strongly suggestive of AA amyloidosis secondary to RA as the cause for dysautonomia in this patient.

Gustatory sweating is a unique neurological dysfunction. Three forms of nonphysiologic gustatory sweating have been described: idiosyncratic, auriculotemporal (Frey's syndrome), and diabetic. The idiosyncratic form occurs after ingestion of one or more specific foods, e.g., cheese or chocolate. Sweating occurs about the face and neck and is profuse, symmetrical, and often accompanied by a flush. The mechanism responsible for this condition is unknown. Many consider it to be a variant of the physiologic form. Frey's syndrome typically evolves as a complication of surgery and/or injury to the parotid or salivary glands.[7] Frey discovered this syndrome in 1923, and it develops postoperatively in 13%–60% of patients undergoing parotidectomy. It may develop weeks or even years after surgery or injury to the parotid gland. Frey's syndrome has also been reported as a sequela of herpes zoster infection, salivary gland removal, condylar fracture, and as a complication of both Pancoast's tumor and combined modality therapy for cancer of the neck. Frey's syndrome is characterized by localized rather than symmetrical gustatory sweating. Both hyperhidrosis and flushing occur over the facial area supplied by the auriculotemporal nerve. In this syndrome, injury to the auriculotemporal nerve is thought to lead to an intermingling and reanastomosis of lacrimal parasympathetic secretomotor nerves with sympathetic sudomotor fibers directed to the skin about the ear and temple.[7] Support for this concept comes from the observation that surgical

ablation of the secretomotor nerve fibers to the parotid gland abolishes the abnormal sweating pattern.[14] Diabetic gustatory sweating has been described in detail.[15] The incidence of diabetic gustatory sweating is unknown, but such patients with diabetes mellitus often also have peripheral neuropathy. The etiology of diabetic gustatory sweating is unclear. Taking these facts into consideration, the pattern of sweating in the present case resembled that of Frey's syndrome, but the gustatory sweating in the patient was markedly different from that of Frey's syndrome in terms of its etiology. Therefore, the most likely explanation is that amyloidotic gustatory sweating is a fourth type of nonphysiologic sweating.

To explain dysautonomia in RA, the hypothesis of a rheumatoid vasculitis has been proposed.[4] Since peripheral RA neuropathies can be related to vasa nervorum vasculitis, it seemed natural to consider that this pathological process extends to the amyelinic autonomic fibers. However, such an autonomic nervous system involvement has never been confirmed histologically and concurrently no dysautonomia has been reported in RA with vasculitis. Our patient had no symptoms of rheumatoid vasculitis. Dysautonomia has also been reported in other collagen vascular diseases such as systemic lupus erythematosus,[4] systemic sclerosis,[5] or Sjögren's syndrome.[16] Gold salt can also sometimes induce autonomic disturbances such as orthostatic hypotension, blood pressure changes, excess sweating, and tachycardia.[4] However, our patient did not undergo gold therapy. An immunological mechanism could also potentially cause dysautonomia with RA and other collagen vascular diseases. This hypothesis has been supported by an experimental animal model of dysautonomia,[4] in which circulating autoantibodies were found that were directed to the autonomic nervous system, but only after injection into the animal of human sympathetic ganglion antigens. The last hypothesis, linking amyloidosis to dysautonomia in RA, is supported by a few previous reports.[4,5] An uncommon case with severe dysautonomia as a consequence of amyloid deposit infiltrating the nervous system has been described.[1] The present case is the first documented to have the SAA1.3 allele, which is a remarkable risk factor for amyloidosis in Japanese RA.[9]

Autonomic nervous system involvement is uncommon in RA. In patients with AA amyloidosis secondary to RA, it seems likely that autonomic nerve dysfunction is a typical symptom in the end stage of the disease and gustatory sweating could be useful as a clinical sign. Further studies correlating dysautonomia with the occurrence of amyloidosis in RA will clarify the frequency and importance of gustatory sweating as a hallmark of autonomic nervous system involvement.

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