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MELKERSSON-ROSENTHAL SYNDROME: LYMPHOSCINTIGRAPHY-DOCUMENTED IMPAIRMENT AND RESTORATION OF FACIAL LYMPHATIC DRAINAGE IN THE COURSE OF DISEASE

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ABSTRACT

Melkersson-Rosenthal syndrome (MRS) is an idiopathic, rare disorder manifested by facial swelling, congenital plicated tongue and recurrent peripheral facial nerve palsy. Labial involvement alone is referred to as cheilitis granulomatosa. Differential diagnosis of MRS includes allergic angioedema, bacterial, viral or filarial infections as well as autoimmunological inflammation in the course of systemic lupus erythematosus, dermatomyositis, and others. We present 4 patients who experienced periodically painless edema of the face and/or lips. Lesions were diagnosed as recurrent Quincke's edema and were treated with antihistamine agents and glucocorticoids without improvement.

In all four cases of MRS, we were able to document impaired lymphatic drainage from the swollen area using lymphoscintigraphy. We also documented in follow-up lymphoscintigraphy a restoration of lymphatic flow in three of the four patients with MRS and these results corresponded with clinical improvement. We have demonstrated that lymphatic pathology plays an important role in pathophysiology of chronic facial swelling in patients with Melkersson-Rosenthal syndrome.

Keywords: Melkersson-Rosenthal syndrome, cheilitis granulomatosis, orofacial granulomatosis, lymphoscintigraphy, facial lymphedema

Melkersson-Rosenthal syndrome (MRS) is a rare, chronic disease of unknown cause with a largely unknown natural history. The disease, consisting of focal inflammation confined to the soft tissues of the face, causes a painless, asymmetrical swelling of the upper and the lower lip (macrocheilitis granulomatosa) and the eyelids (orofacial granulomatosis), and less frequently the tongue, cheek mucosa, throat, or submandibular glands (1,2). Approximately 30% of patients additionally manifest facial paralysis and incidentally other cranial nerves are also affected resulting in impairment of hearing, taste, and smell (3). In 20-40% of cases, furrowed tongue (lingua plicata) is observed and slight regional lymphedema occurs in 50% of the patients (4,5). The classic triad – swelling of the lip, inflammation of VII nerve, and macroscopic changes of the surface of the tongue – is rare. The much more frequent form of the disease is the monosyptomatic cheilitis granulomatosa known as Miescher syndrome (6).

The symptoms of MRS are uncharacteristic and are often mistaken for Quincke's edema caused by food, drug, or contact allergens. They may be also mistaken for post-traumatic symptoms or reactive symptoms triggered by local inflammatory conditions. In fact, all the diagnostic possibilities, including specific inflammations of the lips (tuberculosis, leprosy, infectious mononucleosis, American trypanosomiasis – Chagas disease, and filarial infections such as *Wuchereria bancrofti* and *Brugia malayi*) and connective tissue disease (systemic lupus erythrematosus, dermatomyositis, scleroderma, and Sjoegren syndrome), should be taken into consideration in differential diagnosis. Periorbital edema is also often present as a manifestation in thyroid disease.

Among the above mentioned conditions, MRS is marked by its characteristic histopathological changes. Typically small, non-necrotic granulomas can be observed in the tissue occluding blood vessels, in the vessel wall, within the vessel lumen, and sometimes also within the cervical lymph nodes (4,7). The dominant cell types in the cellular infiltration are histiocytes, plasmocytes, and lymphocytes. Similar histopathological changes also occur in sarcoidosis and non-specific intestine inflammations, e.g., Crohn's disease. These histopathological changes suggest similarities in the pathogenesis and possibly coexistence of the other conditions and should prompt investigation of MRS patients for lesions within the lungs and gastrointestinal tract. This histopathological picture, although characteristic of MRS, cannot always be documented. So far, no other anomalies typical of MRS have been reported.

Among patients manifesting facial edema admitted to University Hospital, Department of Allergology of the Medical University of Wroclaw, between January 2005 and December 2007, 4 patients were diagnosed as Melkersson-Rosenthal Syndrome including the oligo (3 patients) and monosymptomatic forms (1 patient). Diagnosis was established on basis of a set of characteristic clinical symptoms: recurrent and with time chronic edema of the upper lip, incidents of facial nerve inflammation, and/or macroscopic changes of the surface of the tongue. All patients had been previously unsuccessfully treated for allergic conditions with anti-histaminic drugs. In all 4 cases, differential diagnosis was carried out to eliminate allergic, auto-immune and reactive character of the facial changes. Additionally, lympho-scintigraphy was performed to assess the facial lymphatic drainage on admission and at follow-up. We present clinical reports of the 4 cases.

CASE HISTORIES

Case 1

A 52 year-old women was admitted to the hospital with an 8-month history of recurrent left-sided facial edema with nose reddening. She had a history of recurrent labial herpes for 30 years, left eye redness for two years, and left facial nerve palsy for the past month. General physical examination revealed no signs of acute or chronic distress with left-sided lip, cheek, and upper eyelid edema visible (*Fig. 1*). Partial dental prosthesis and a plicated tongue were observed. No signs of cranial nerve disturbances were observed. Laboratory work-up revealed no abnormalities. Allergy (skin prick tests with basic aero- and food allergens, skin patch tests) and auto-immune disease [antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA)] were excluded and the diagnosis of Melkersson-Rosenthal syndrome was established. Initial lymphoscintigraphy, performed with bilateral upper lip injection of radiotracer (0.25 mCi ^{99m}Tc-Nanocoll), revealed no visualization of regional lymph nodes 2 hours after injection (*Fig. 2A*).

At follow-up evaluation 3 years later, the patient reported less intense symptoms, with aggravation after sweets, especially on the left side of the face with forehead, eyelid, cheek, and upper lip edema and redness. Follow-up

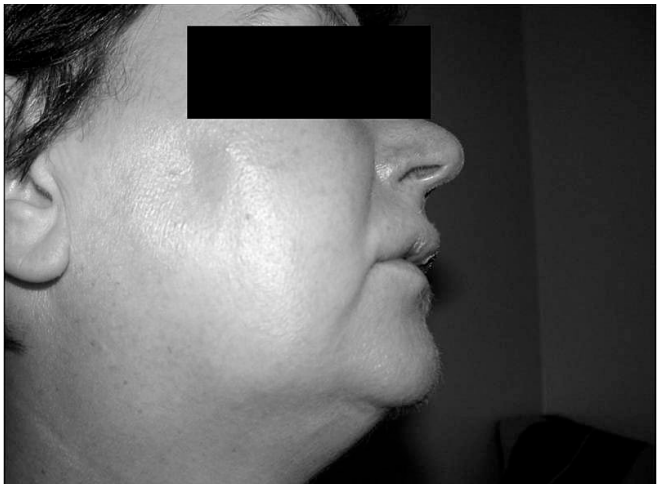

Fig. 1. Upper lip and cheek swelling in demonstrated in a patient with Melkersson-Rosenthal syndrome (Case 1).

lymphoscintigraphy 2 hours after injection visualized bilateral submandibular lymph nodes (predominant on the right). Compared to initial lymphoscintigraphy, a significant improvement of lymphatic drainage was seen with restoration of lymph flow to regional lymph nodes *(Fig. 2B*).

Case 2

A 59 year-old woman was admitted to the hospital with upper lip edema. Symptoms were periodic with slight remission and had lasted for 7 months, alternately affecting the left and right side of the face with a feeling of formicating. She did not correlate the symptoms to any known factors and reported neither labial herpes nor facial nerve palsy. She consulted a dentist, oncologist, dermatologist, and angiologist without a definitive diagnosis, and none of the medications prescribed (antihistamines, antibiotics, pentoxifylline) succeeded. She stopped all therapy. General physical examination revealed no signs of acute or chronic distress with pale edema of the upper lip, no visible tongue plication and dental caries under treatment. Laboratory work-up revealed slightly increased total cholesterol level (5.3 mmol/l, normal range (n.r.) 3.1 -5.2 mmol/l) and triglycerides (2.0 mmol/l, n.r. 0.4 - 1.8 mmol/l). Allergy (skin prick tests with basic aero-allergens, total and specific IgE, blood and nose-swab eosinophilia) and autoimmune disorders (ANA, ANCA, complement hemolytic activity, C3 and C4 level) were excluded and the diagnosis of Melkersson-Rosenthal syndrome was made. Initial lymphoscintigraphy performed with bilateral upper lip injection of radiotracer revealed no visualization of regional lymph nodes 2 hours after injection (*Fig. 3A*).

At follow-up evaluation 1.5 years later, the patient presented with a reduction of symptoms compared to the initial visit and reported periodic complete remissions. Physical examination revealed slight pale edema of the upper lip. Follow-up lymphoscintigraphy was performed with bilateral subcutaneous upper lip injection of radiotracer. 2 hours after injection, submandibular lymph nodes were visualized on the left side and in the midline, documenting significant improvement of lymphatic drainage compared to the initial examination (*Fig. 3B*).

Case 3

A 34-year-old woman was admitted to the hospital with a 4-year history of upper

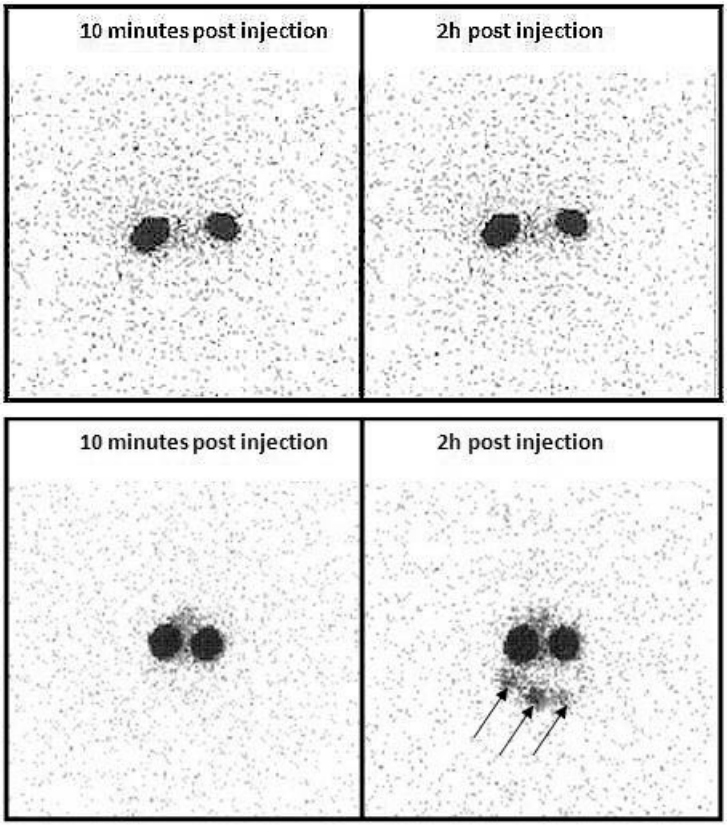

Fig. 2. A) Initial lymphoscintigraphy after bilateral injection of tracer into the lips (Case 1). B) Follow-up bilateral lymphoscintigraphy after 3 years demonstrating visualization of local lymph nodes (arrows).

lip swelling. Initially, edema was transient persisting for approximately 2 weeks. After 1.5 years, it became persistent despite medication (antihistamines, oral corticosteroids). Ten years earlier she had suffered from right facial nerve inflammation. Other complaints included excessive morning lacrimation, periodic hand eczema, and recurrent labial herpes. General physical examination revealed no signs of acute or chronic distress with asymmetric, right upper labial edema and no signs of cranial nerves disturbances. Laboratory work-up revealed elevated fibrinogen concentration (> 8.4 g/l, (n.r.) 1.8 - 3.8 g/l) and erythrocyte sedimentation rate of 22 mm and 33 mm after 1 hour. Allergy (skin prick tests with basic aero- and food allergens), auto-immune disease (ANA, complement hemolytic activity), and congenital disorders (C1 esterase inhibitor activity) were excluded. A labial biopsy was performed and chronic labial inflammation, partially granulomatous, was described. The diagnosis of Melkersson-Rosenthal syndrome was established. Initial lymphoscintigraphy, performed after a unilateral right subcutaneous injection in the upper lip, demonstrated no transport of the tracer at 10 minutes or 2 hours after injection and no visualization of regional lymph nodes at 2 hours after injection. These findings are consistent with significantly impaired lymphatic drainage from the affected area (*Fig. 4A*).

At follow-up evaluation 1 year later, the patient appeared with no general signs of acute or chronic distress and with persistent, asymmetric, slight right upper labial edema. Follow-up lymphoscintigraphy, performed

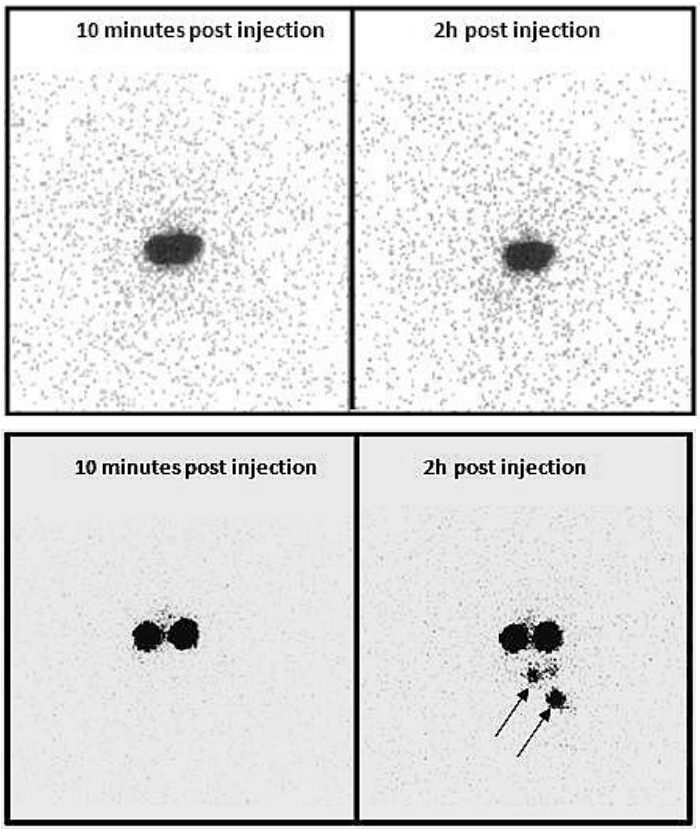

Fig. 3. A)) Initial lymphoscintigraphy after bilateral injection of tracer into the lips (Case 2). B) Follow-up bilateral lymphoscintigraphy after 1.5 years demonstrating visualization of local lymph nodes (arrows).

with bilateral subcutaneous upper lip injection of radiotracer demonstrated submandibular lymph nodes visualization on the left side and in the midline 2 hours after injection. This finding may suggest improvement as compared to the initial examination since the initial evaluation was only unilateral on the right (*Fig. 4B*).

Case 4

A 32 year-old man had observed recurrent pale facial edema, lasting for 3-14 days with no pain or itching, with either spontaneous or drug-related (antihistamines, oral corticosteroids) regression for 2-3 years. 6 years before, left facial nerve palsy had been recognized. General physical examination revealed no signs of acute or chronic distress and pale edema of the upper lip, a plicated tongue, and dental caries. Laboratory work-up revealed elevated triglycerides (2.9 mmol/l, n.r. 0.4-1.8 mmol/l), anti-HBs antibodies, anti-HBc antibodies, and no HBs Ag. Gastroscopy revealed duodenal ulcer, which was *H. pylori* positive, and a protocol of *H. pylori* eradication was conducted. Abdominal ultrasound demonstrated hepatic steatosis, and thyroid ultrasound showed a non-homogeneous and calcify nodule. Endocrinology consult and thyroid nodule biopsy revealed no signs of malignancy. Allergy (skin prick tests with basic aero- and food allergens, blood and nose-swab eosinophilia) and autoimmune disease (autologous ANA, ANCA, anti-TPO, anti-cardiolipin antibodies, complement hemolytic activity) were excluded and the diagnosis of

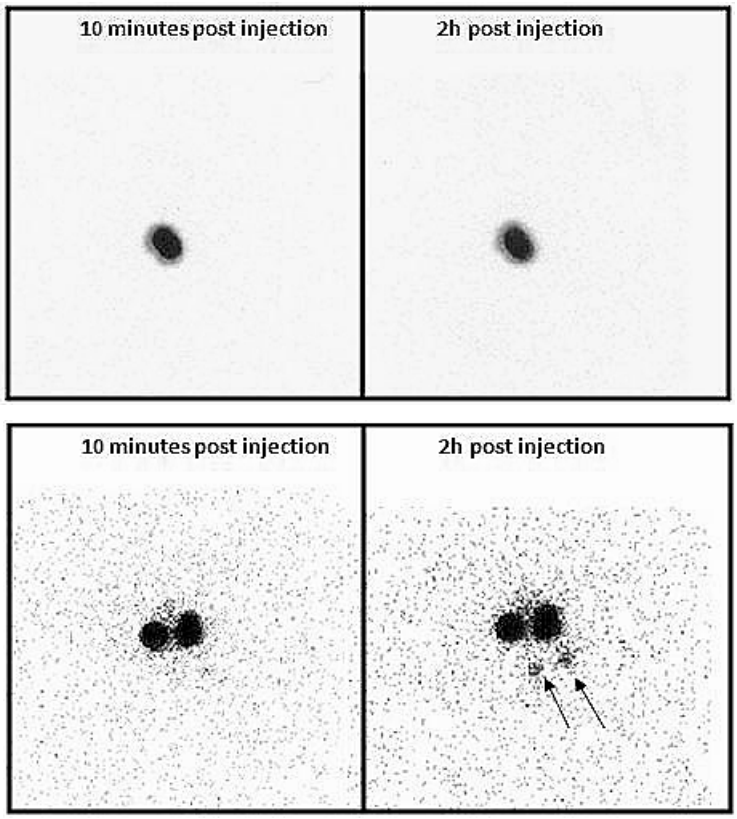

Fig. 4. A) Initial lymphoscintigraphy after unilateral right injection of tracer into the lip (Case 3). B) Follow-up bilateral lymphoscintigraphy after 1 years demonstrating visualization of local lymph nodes (arrows).

Melkersson-Rosenthal syndrome established. Initial lymphoscintigraphy, performed after bilateral upper lip injection of radiotracer, revealed no visualization of regional lymph nodes 2 hours after injection (*Fig. 5A*).

At follow-up evaluation 2 years later, symptoms were reduced (patient was on permanent antihistamine medication), but there was not complete remission. Aggravation was found to occur after viral oto-rhino-laryngological infections. The upper lip edema and plicated tongue remained as before, and the dental caries had been treated. Follow-up lymphoscintigraphy, performed after bilateral upper lip injection of radiotracer, revealed no visualization of regional lymph nodes 2 hours after injection, and no improvement compared to the initial examination was observed (*Fig. 5B*).

DISCUSSION

The orofacial granulomatoses comprise a group of conditions with clinical and pathological similarities consisting of lip and oral cavity swelling and granulomatous inflammation. There are many diseases in the differential diagnosis including inflammations (*Trichinella spiralis*, *Loa loa*, *Brugia malayi*, *Trypanosoma cruzi*, *Mycobacterium leprae*), autoimmunological diseases (thyroiditis, Crohn's disease), systemic diseases of the connective tissue (systemic lupus erythematosus, dermatomyositis), and edema angioneutroticum (Quincke). MRS differs from these other disorders by its lack of unequivocally defined causal factors, symptoms confined to the face and oral cavity, and its long-lasting course marked by

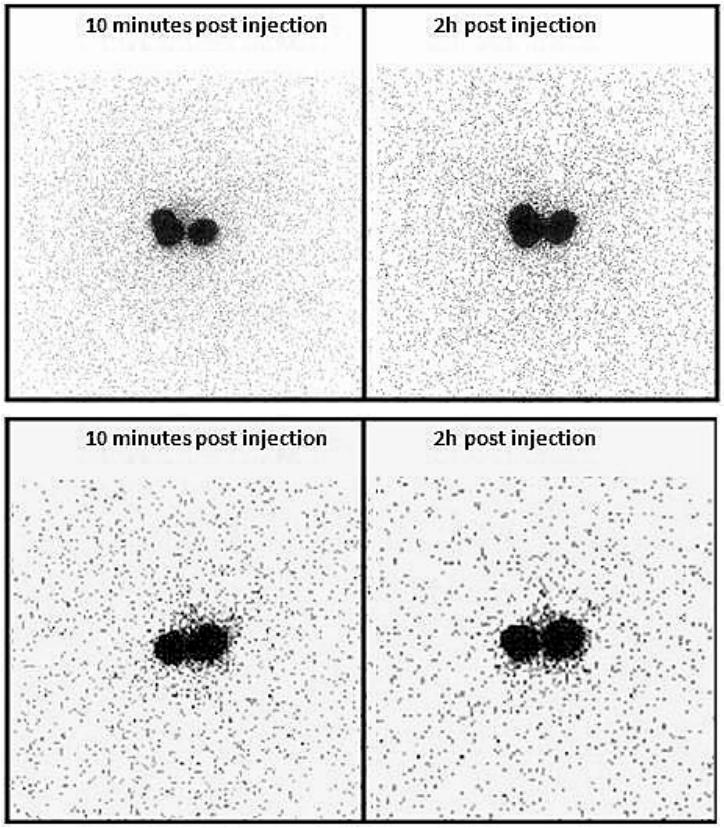

Fig. 5. A) Initial lymphoscintigraphy after bilateral injection of tracer into the lips (Case 4). B) Follow-up bilateral lymphoscintigraphy after 1.5 years demonstrating no improvement.

remissions and recurrences. No characteristic genetic, immunological, or histological features of MRS have been discovered, which necessitates the performance of a wide panel of diagnostic tests to eliminate the possibilities of other diseases that also manifest by swelling of the eyelids, mouth and oral cavity. Therefore, all clinical observations broadening the knowledge abort MRS symptomatology and its peculiarities are of a great value.

We have demonstrated that lymphatic pathology plays an important role in pathophysiology of chronic facial swelling in patients with Melkersson-Rosenthal syndrome. In all four cases of MRS, we documented impaired lymphatic drainage from swollen area with lymphoscintigraphy. This finding confirms earlier observation of Ohkuma, who observed delayed albumin tissue clearance from the swollen lip in patients with cheilitis granulomatosa (8). Cockerham et al also found that MRS is characterized histopathologically by a granulomatous lymphangitis and this finding seems to be unique to this condition (9). We also documented with follow-up lymphoscintigraphy, a restoration of lymphatic flow in three of four patients with MRS, and these results corresponded with clinical improvement.

We believe that these findings are important for two reasons. Firstly, because we have documented that Melkersson-Rosenthal syndrome represents a type of facial lymphedema. Secondly, we have observed restoration of lymphatic flow with improvement of edema which may be the

first observation of spontaneous restoration of lymphatic drainage and alleviation of lymphedema. We can hypothesize that the nature of lymphatic pathology is different in MRS than in idiopathic lymphedema allowing restoration of lymphatic flow. Restoration of lymphatic flow has been documented previously in cases of mechanical or surgical dissection of lymphatic vessels or lymph nodes e.g., in patients undergoing limb replantation surgery (10) and in women who underwent axillary lymph node dissection (Szuba A, unpublished data). However, restoration of lymphatic flow in patients with idiopathic lymphedema has not been reported. Histopathological findings suggest occlusion of lymphatic vessels in the affected area by epithelioid granulomas within the vessel lumen (9). In idiopathic lymphedema we can see obliteration of lymphatic trunks with intimal hyperplasia (11) and dilated lymphatic channels in the skin or aplasia of initial lymphatics (12). It is possible that restoration of lymph flow is accompanied by resolution of intralymphatic granulomas; however, this theory would require histological confirmation, which would have no clinical value to the patient.

Although this small series is informative, there are many questions that remain, and the clinical course of MRS is still not understood. In our series, we demonstrated two patients (Cases 1 and 2) in whom edema reduced over time and the imaging improved. Another patient (Case 3) showed no improvement in the edema but an improved imaging and a patient (Case 4) with an improvement in edema without improvement in imaging. There is a possibility that the clinical course changes more rapidly (maybe in response to aggravating factors as in Cases 1 and 4) than our follow-up assessments can follow. A very precise and frequent examination of patients with MRS over longer time periods may ultimately be needed to better understand the nature of the disease.

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