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Commentary

The Lingual Ternion-Melkersson-Rosenthal Syndrome

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Received: November 19, 2021; **Published:** January 17, 2022

Preface

Melkersson-Rosenthal syndrome is an exceptional, recurrent, progressive neuro-muco-cutaneous disorder which is characteristically comprised of orofacial oedema, fissured or plicated tongue and facial nerve paralysis. Clinical syndrome of Melkersson-Rosenthal syndrome constituted of orofacial oedema, facial nerve palsy and plication or furrowing of the tongue was initially scripted by Ernst Gustaf Melkersson and Rosenthal in 1928 and 1931 respectively [1,2].

Although infrequent, the clinical trilogy of reoccurring facial nerve paralysis, orofacial oedema with singular or bilateral swelling of lips or cheilitis granulomatosa and furrowing or fissuring of tongue or lingua plicata constitutes the syndrome.

When devoid of a specific aetiology, Melkersson-Rosenthal syndrome may be denominated as cheilitis granulomatosa, granulomatous cheilitis or mono-symptomatic Melkersson-Rosenthal syndrome. Thus, preliminary disease discernment and appropriate therapy is necessitated to circumvent unsought for, disease- associated complications.

Disease characteristics

Melkersson-Rosenthal syndrome commences in childhood or adolescence. Disease onset may occur up to 14 years wherein median age of disease discernment is 4 years to 9 years. However, cogent detection may be delayed and the condition may manifest up to seventh decade [3,4].

Clinical symptoms of adult onset disease are common between 25 years to 40 years. A female predominance is observed with a female to male proportion of 2:1 [3,4].

The syndrome may represent with initial singular, pertinent clinical symptoms. Following an extensive, frequent or repetitive emergence of clinical symptoms, orofacial oedema may persist, enhance and manifest as a constant feature [3,4].

Of obscure aetiology, Melkersson- Rosenthal syndrome may emerge as a genetic condition wherein several members of a single family appear implicated. Additionally, factors such as dietary habits, exposure to allergens, viral infections as with herpes simplex virus (HSV), immune deficient states or stress may contribute to disease emergence [3,4].

Additionally, the paediatric disorder may be associated with herpes simplex 1 viral (HSV1) infection, hereditary granulomatosis, mycobacterial infection as tuberculosis or leprosy, chronic infection, Down's syndrome, psoriasis, thyroiditis, multiple sclerosis, keratitis, Wegener's granulomatous, diabetes mellitus, sarcoidosis, ulcerative colitis or allergic disorders. Genetic mutation with UNC-93B deficiency may predispose to herpes simplex 1 viral (HSV1) infection [3,4].

Respiratory infection with influenza virus may trigger relapsing Melkersson-Rosenthal syndrome [3,4].

Chromosomal mutation of FATP1 (fatty acid transport protein) may occur or the condition may be transmitted as an autosomal dominant disorder. Incriminated individuals depict anomalous immune functions, immune deregulation or allergic tendencies [3,4].

Clinical elucidation

Commonly, clinical representation may be oligo-symptomatic or mono-symptomatic. Initial clinical manifestation emerges as oedema of upper lip, lower lip or both lips, eyelids or singular segment of scalp. Upper lip is frequently incriminated. Lips appear hardened, cracked, fissured and depict a reddish brown discolouration.

Additionally, fissures upon dorsum of tongue may appear. Intraoral examination demonstrates macroglossia and deep-seated fissures upon dorsal or lateral surfaces of the tongue [5,6].

Facial paralysis of significant duration may ensue. A frequent, initial clinical symptom of Melkersson-Rosenthal syndrome is orofacial oedema. Isolated facial nerve palsy or singular oedema of the eyelids may be challenging to classify. Fissured tongue may appear at birth and is observed in around 20% to 40% individuals [5,6].

Generally, facial nerve palsy is a preliminary clinical symptom and precedes orofacial oedema by a significant period. Facial palsy may be unilateral or bilateral and may be associated with facial oedema [5,6].

Occurrence of facial nerve palsy enhances with progressive disease and is discerned in around 30% subjects [5,6].

Orofacial oedema may be reoccurring and subsides within the preliminary stage. Nevertheless, oedema of orofacial tissue may persist and become perpetual. Orofacial oedema is painless, non-pitting and commonly occurs within the upper limbs, upper arms, lower lip, tongue, buccal mucosa, eyelids, gingiva, neck, nose, genitalia or the larynx. Partial persistence or non resolution of oedema may initiate facial fibrosis with permanent disfiguration of the face [5,6].

Fissured tongue or lingua plicata may be hereditary and is categorized as grooved dorsum of tongue wherein grooves are of minimal 15 millimetre magnitude and 2 millimetre depth. Fissured tongue engenders secondary infections, hypertrophy, decimated papillae, dysgeusia and dysesthesia [5,6].

Additionally, neurological symptoms such as tinnitus, deafness, facial paraesthesia, dysphagia, hypogeusia, conjunctival congestion, aphthous ulcers, decreased or excessive facial sweating, excessive lacrimation and visual disturbances may be discerned. Trigeminal, olfactory, auditory, glossopharyngeal or hypoglossal cranial nerves may be implicated [5,6].

Non-neurological clinical symptoms are comprised of uveitis, diverticulitis or ulcerative colitis. Repetitive Melkersson-Rosenthal syndrome may engender personality changes, anxiety or depression [5,6].

Oligo-symptomatic variant is comprised of representation of dual clinical features. Additionally, histological evidence of granulomatous cheilitis within the eyelid or lip is contemplated as a diagnostic feature [5,6].

Mono-symptomatic variant describes the occurrence of a singular clinical symptom as non-necrotising, cheilitis granulomatosa discernible in subjects with isolated facial or lip oedema, a condition denominated as Miescher's cheilitis [5,6].

Classic clinical triad associated with Melkersson-Rosenthal syndrome as reoccurring facial nerve paralysis, orofacial oedema with singular or bilateral swelling of lips or cheilitis granulomatosa and furrowing or fissuring of tongue or lingua plicata is discernible in roughly ~70% subjects. Thus, appropriate disease discernment may be challenging. For cogent determination, Melkersson-Rosenthal syndrome necessitates the presence of aforementioned clinical symptoms [5,6].

Histological elucidation

Classically, cheilitis granulomatosa is composed of oedema and dilatation of lymphatic vessels confined to the superficial lamina propria. Aggregates of non-caseating granulomas, constituted of small, mature lymphocytes and histiocytes, appear disseminated within the oedematous, orofacial lamina propria or stromal tissue confined to the lip [7,8].

Certain instances of acute disease depict vascular articulations circumscribed by lymphocytic infiltration whereas distinctive epithelioid cell granulomas may be absent [7,8].

Melkersson-Rosenthal syndrome requires a segregation from granulomatous inflammatory conditions as sarcoidosis or Crohn's disease [7,8].

Inflammatory bowel disease as Crohn's disease may manifest oral features as lip swelling, fissured lips, mucositis, gingivitis, glossitis or cobblestone appearance of oral mucosa [7,8].

Therapeutic options

Therapeutic alleviation of the exceptional syndrome is challenging. Symptomatic instances can be treated with nonsteroidal anti inflammatory agents (NSAIDs), corticosteroids, antibiotics or antidepressant agents [9,10].

Melkersson-Rosenthal syndrome is devoid of a specific therapeutic strategy wherein administration of corticosteroids appears as an optimal treatment option [9,10].

Intra-lesional triamcinolone acetonide or betamethasone can be employed to decimate severity of localized orofacial oedema or circumvent reoccurring orofacial oedema and may alleviate cheilitis granulomatosa in the absence of systemic disease [9,10].

Lignocaine is employed prior to intra-lesional corticosteroids in order to decimate pain [9,10].

Corticosteroids along with minocycline or roxithromycin generates an anti-inflammatory response [9,10].

Nutritional supplements and vitamins as thiamine, niacin, riboflavin, pyridoxine, ascorbic acid or vitamin E may be utilized along with corticosteroids. Adoption of pertinent measures as benzoate free diet, cinnamon-free diet or acyclovir remains debatable [9,10].

Molecules such as adalimumab or infliximab may be advantageous in treating steroid-refractory lip oedema or orofacial granulomatosis [9,10].

Refractory or reoccurring Melkersson-Rosenthal syndrome can be appropriately treated with immunosuppressive agents as methotrexate or thalidomide [9,10].

Surgical procedures as total or subtotal facial nerve decompression are optimal in alleviating refractory, repetitive facial nerve palsy.

Surgical intervention for treating persistent lip oedema can be beneficially adopted. Cheiloplasty is advantageous following failure of triamcinolone acetonide. Laser ablation may be utilized instead of cheiloplasty. However, proportionate disease reoccurrence remains unaltered [9,10].

Although debatable, surgical intervention may be adopted in order to decimate compression of facial nerves and orofacial oedema. Irrespective of category of treatment, regular monitoring of the chronic, progressive syndrome is recommended despite an absence of associated clinical symptoms [9,10].

Complications of Melkersson-Rosenthal syndrome appear as sinusitis, candidiasis, facial erythema, IgA nephropathy, vitiligo, thyroid hormonal anomalies or lacunar stroke [9,10].

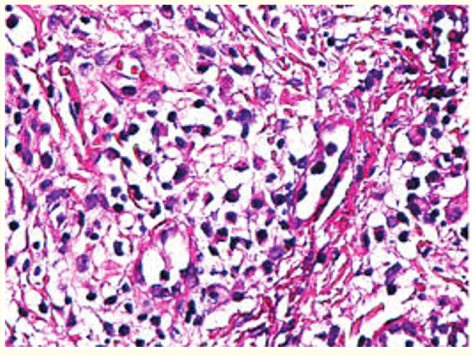

Figure 1: *Melkersson-Rosenthal syndrome depicting dilated lymphatic channels admixed with a chronic inflammatory exudate of lymphocytes and macrophages with ill-formed epithelioid cell granulomas [11].*

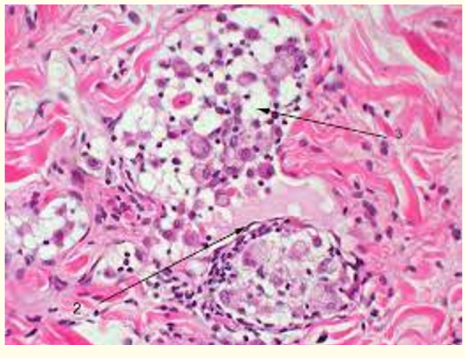

Figure 2: *Melkersson-Rosenthal syndrome delineating non caseating epithelioid cell granulomas admixed with lymphocytes, macrophages within a fibrotic stroma [12].*

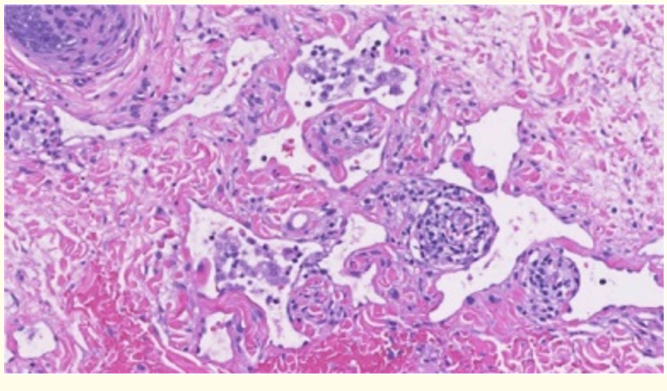

Figure 3: *Melkersson-Rosenthal syndrome demonstrating several epithelioid cell granulomas intermingled with numerous lymphocytes, macrophages and dilated lymphatic articulations [13].*

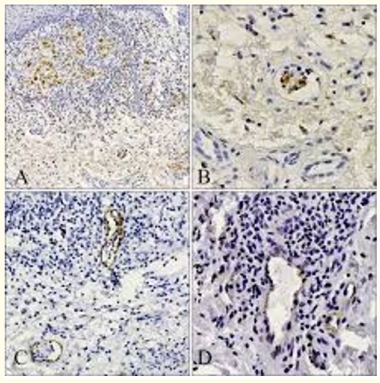

Figure 4: *Melkersson-Rosenthal syndrome exhibiting numerous, small epithelioid cell granulomas intermixed with an intense infiltrate of lymphocytes and macrophages [14].*

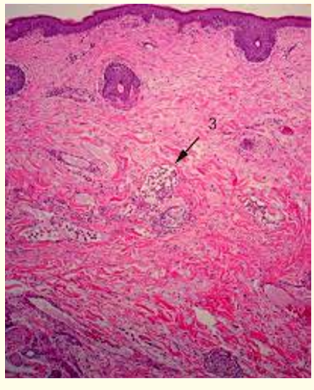

Figure 5: *Melkersson-Rosenthal syndrome exemplifying disseminated non caseous epithelioid cell granulomas with a patchy, chronic inflammatory cell exudate and a superimposed strip of stratified squamous epithelium [12].*

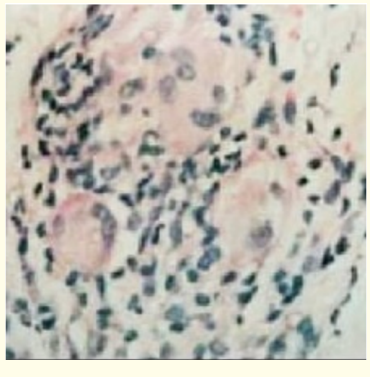

Figure 6: *Melkersson-Rosenthal syndrome exemplifying disseminated non caseous epithelioid cell granulomas with a patchy, chronic inflammatory cell exudate and a superimposed strip of stratified squamous epithelium [12].*

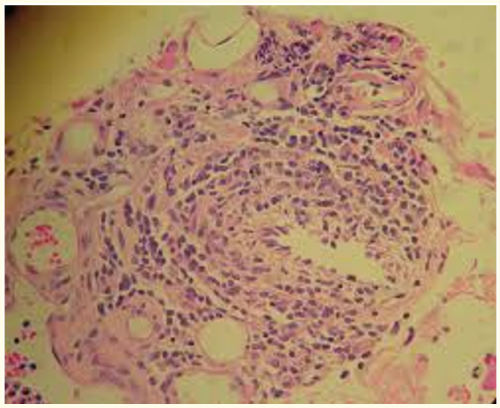

Figure 7: *Melkersson-Rosenthal syndrome exhibiting epithelioid cell granuloma circumscribed by an intense inflammatory cell exudate of lymphocytes and histiocytes [16].*

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11. Image 1 Courtesy: Iranian Journal of Dermatology.

12. Image 2 and 5 Courtesy: Ocular pathology.

13. Image 3 Courtesy: Wiley online library.

14. Image 4 Courtesy: Europe PMC.

15. Image 6 Courtesy: ijdvl.com.

16. Image 7 Courtesy: Annals of allergy, asthma and immunology.

Volume 21 Issue 2 February 2022