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Item Type	Journal Article
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Citation	<p><p>Makarenko VV, Vaezi AE, Brettler DB, Hutchinson L, Woda BA, Chen BJ. Laryngeal mucous membrane plasmacytosis with 15 year follow-up: Case report and literature review. Leuk Res Rep. 2019 Nov 27;13:100190. doi: 10.1016/j.lrr.2019.100190. PMID: 31867207; PMCID: PMC6906643. Link to article on publisher's site</p></p>
DOI	10.1016/j.lrr.2019.100190
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Download date	2026-06-16 11:47:48
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Link to Item	https://hdl.handle.net/20.500.14038/41347



Laryngeal mucous membrane plasmacytosis with 15 year follow-up: Case report and literature review



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ARTICLE INFO

Keywords:

Mucous membrane plasmacytosis
Long-term follow-up

ABSTRACT

Mucous membrane plasmacytosis (MMP) is an uncommon variant of mucositis represented by a polyclonal plasma cell infiltration of mucosal tissue. Various clinical presentations in the upper airway have been reported ranging from erythematous mucosa to fungating masses. Histologic features include mucosal epithelial hyperplasia or psoriasiform changes with a dense submucosal infiltrate of polytypic plasma cells. Molecular studies for immunoglobulin gene rearrangement should be performed in all cases of MMP to rule out clonal neoplastic expansion of plasma cells. We present a case of MMP with over 15 years of clinical follow-up, emphasizing the relatively benign clinical course of this disorder.

1. Introduction

Mucous membrane plasmacytosis (MMP) is a rare variant of mucositis represented by a polyclonal plasma cell infiltration of the tissue. The diagnosis can be challenging considering significant histological similarities with neoplastic lesions. About 50 cases have been reported in the English literature including less than 10 published cases with long (more than 5 years) follow-up [1–6]. The first evidence of unusual plasma cell infiltrate was described in glans penis by Zoon in 1952 which he termed a “chronic benign balanoposthitis with plasmacytes” [7]. Clinicopathologically similar process was later identified in orofacial mucosa by Schuermann [8] and Luders [9], and was originally named plasmacytosis circumficialis. Since then, multiple terms were introduced including plasmacytosis mucosae, plasma cell orificial mucositis, plasma cell mucositis, and MMP, however no consensus in terminology still exists. Exceedingly rare cases of cutaneous and systemic variants of plasmacytosis have been reported in patients of Asian descent but appear to be unrelated to MMP [10].

The etiology of MMP is not clear, but associations with some exogenous factors or immunologically mediated diseases were suggested [2]. Recognition of the entity is important as no progression to plasma cell or other hematological neoplasm was noted. Only one reported case showed concomitant squamous cell carcinoma with unclear etiopathogenetic association [11]. The median age of the patients at

presentation is 60 years old and ranging from 17 to 84 years old. Various clinical presentations have been reported ranging from erythematous surface of mucosa to fungating mass. The major histological features include epithelial hyperplasia or psoriasiform changes with a dense infiltrate of polytypic plasma cells. The plasma cells can present with occasional Russel bodies but show no atypia. Molecular studies for immunoglobulin (Ig) gene rearrangement should be performed in all cases of MMP to rule out clonal expansion of plasma cells. Here we present a rare case of MMP with over 15 years follow-up.

2. Case report

We report a case of a 68-year-old female with a history of chronic obstructive pulmonary disease and smoking, who presented with a long history of dysphagia due to a persistent laryngeal lesion, first identified in 2002. A biopsy of the laryngeal lesion in 2002 showed a submucosal plasmacytosis. Definitive evidence of clonality was not seen by immunohistochemical (IHC) or molecular testing. The patient had normal immunoglobulin levels and serum protein immunofixation was negative for monoclonal proteins. Complete blood count and chemistry tests were within normal limits. Serum protein studies showed free kappa and lambda light a chain within normal limits, no monotypic immunoglobulin band on immunofixation electrophoresis was seen. No additional masses were identified. The patient had localized cervical

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<https://doi.org/10.1016/j.lrr.2019.100190>

Received 14 March 2019; Received in revised form 13 November 2019; Accepted 23 November 2019

Available online 27 November 2019

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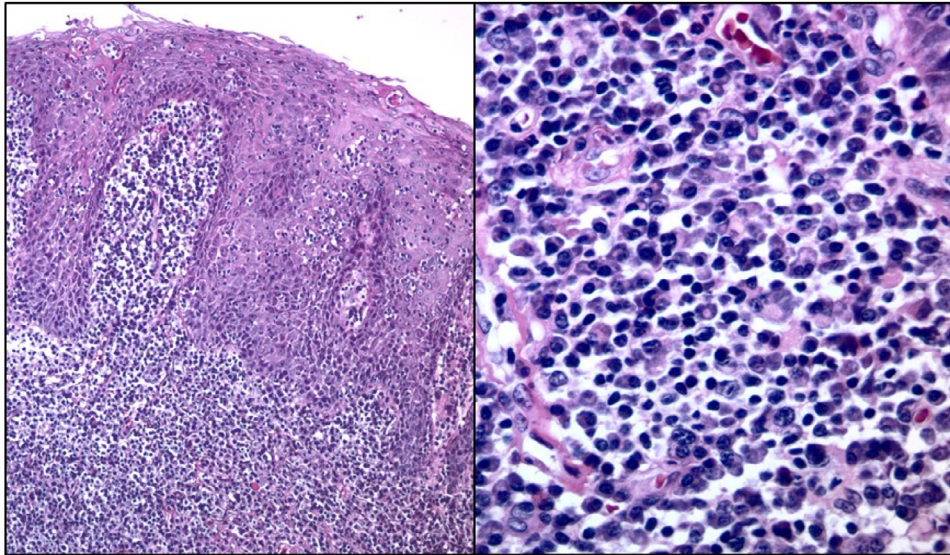


Fig. 1. Hematoxylin-eosin stain demonstrating hyperplastic epithelium with plasma cells rich underlying lamina propria. A. ($\times 100$ magnification). B. Prominent, dense, subepithelial infiltrate composed primarily of mature plasma cells without atypia and rare Russel bodies ($\times 400$ magnification).

lymphadenopathy in 2002 that was biopsied to reveal a benign reactive lymph node. The patient was treated with low dose prednisone which relieved the dysphagia in 2002. The patient experienced a waxing and waning course over the next 15 years that was fairly responsive to steroid therapy. She recently re-presented in 2017 with mild enlargement of a papillomatous laryngeal lesion, no monoclonic immunoglobulin band on immunofixation electrophoresis was seen, and a repeat biopsy of the lesion was performed.

The histological findings were similar between the 2002 and 2017 biopsy. The sections from the laryngeal biopsies showed squamous mucosa with nodular psoriasiform epithelial hyperplasia (Fig. 1). No dysplasia was seen. There was neutrophilic inflammation of the epithelium with occasional microabscesses. A prominent, dense, sub-mucosal infiltrate composed primarily of plasma cells was present. Plasma cells appeared mature with round nuclei and without prominent nucleoli. IHC studies showed that the plasma cells were positive for

CD138 (variable expression) and CD38; and negative for CD56, CD20, cyclin D1 and HHV8 (Fig. 2). Kappa and lambda IHC and in-situ hybridization (ISH) studies showed elevated kappa:lambda ratio, but definitive evidence of monoclonic light chain expression was not seen. EBER ISH was negative. Grocott's methenamine silver (GMS) and spirochete stains were negative for microorganisms. Molecular PCR studies performed in 2002 were negative for clonal immunoglobulin heavy chain (IGH) gene rearrangements. In the biopsy from 2017, PCR studies showed an equivocal gene rearrangement of the IGH gene in a polyclonal background, and no clonal rearrangements of IGK, IGL, and IGK deleting element.

3. Discussion

Few reports are available regarding long-term histopathological and clinical follow-up of mucous membrane plasmacytosis (MMP). In

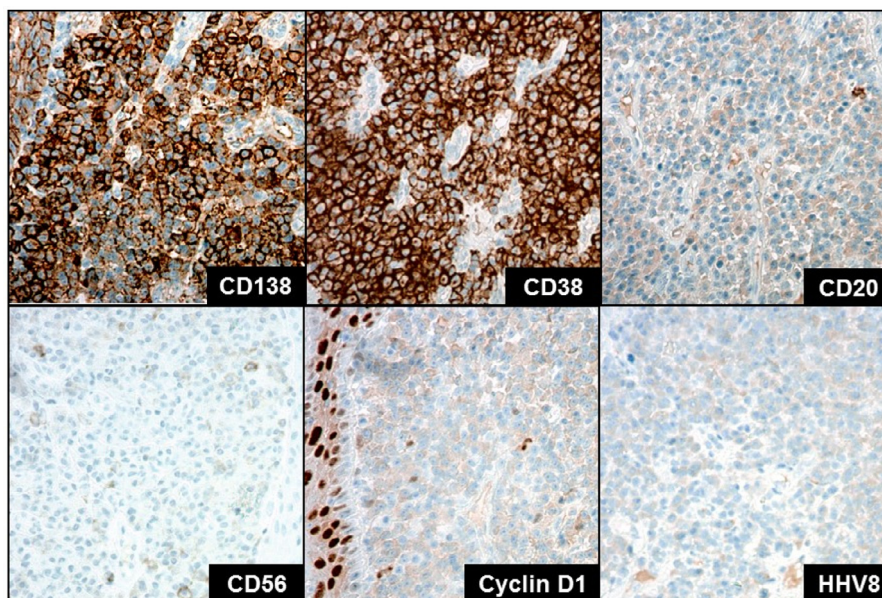


Fig. 2. Selected immunohistochemical stains demonstrated in tumor cells. Positive staining for CD138 and CD38, and negative staining for CD20, CD56, Cyclin D1 and HHV8. ($\times 200$ magnification).

Table 1
Summary of reported cases of mucous membrane plasmacytosis.

Case	Age (years), gender	Location	Presumable etiological factor	Histologic findings	Ancillary studies	Follow up
White et al., 1986	47, F	lips, mouth, tongue, supraglottic larynx	Smoker for 32 years	Epidermal acanthosis with intercellular edema, mild dyskeratosis and exocytosis; dense bandlike infiltrate of plasma cells in the upper dermis	Stained polyclonal for κ and λ light chains as well as β and γ heavy chains	Persistent disease, 9 yrs
Timms et al., 1991	32, F	supraglottis, gingiva, mucobuccal	Not reported	Marked pseudoepitheliomatous hyperplasia with dense, predominantly plasmacytic infiltration of the lamina propria; the plasma cells are mature and lacked pleomorphism	Stained polyclonal for κ and λ light chains and various heavy chains	Persistent disease, 7 y
Grattan et al., 1992	68, M	papillary hyperplasia extending from the hard palate to the uvula	Long-term dentures	Hyperplastic epithelium with a diffuse infiltrate of neutrophils in the deeper layers forming spongiform micro-abscesses in the subcorneal region; dense inflammatory infiltrate in the lamina propria consisting almost entirely of mature plasma cells.	Stained polyclonal for IgG; PAS and GMS stains were negative for fungi.	Persistent disease, 15 y
Ferreiro et al., 1994	41, F	Supraglottic, glottic larynx, nose, pharynx	Not reported	Psoriasiform changes with parakeratosis, elongation of rete ridges, suprapapillary epithelial thinning. Marked dyskeratosis. Dispersed exocytosis and aggregation of PMNs with the epidermis. Munro-microabscess like lesions in 2 cases. Diffuse expanse of inflammatory cells in submucosal tissue composed largely of mature plasma cells with scattered PMNs and lymphocytes. Foamy macrophages are not present. The plasma cells did not show anaplasia, prominent nucleoli or Dutcher body. Occasional Russel bodies are present. No associated endothelial hyperplasia.	Stained polyclonal for κ and λ light chains. Only one case was studied and found to be negative for gene rearrangement in Ig-encoding region. Warthin-Starry, GMS, Gramm stains were negative for microorganisms.	Persistent disease, 7y, tracheostomy
Fogarty et al., 2001	62, F	Supraglottic, glottic larynx, trachea	Not reported			Persistent disease, 16 y, tracheostomy
Galvin et al., 2016	45, F	Supraglottic larynx, lips, mouth, tongue	Not reported			Persistent disease, 9 y
Our case	40, M	Supraglottic, glottic larynx, lips, mouth, tongue, palate, pharynx	Not reported			Persistent disease, 15 years, apnea
	27, F	Gingiva progressed to supraglottic and glottic larynx	Chewing gum	Pseudo-epitheliomatous hyperplasia of the surface epithelium, with a densely cellular infiltrate, almost entirely plasmacytic.	The IHC revealed small amounts of IgA, abundant IgG. Stained polyclonal for κ and λ light chains.	Persistent disease, 21 y
	68 F	Gingival	Long-term dentures	Partly ulcerated squamous epithelium with an underlying dense polyclonal plasma cell infiltrate. No interface mucositis was seen.	Stained polyclonal for κ and λ light chains.	Remission for 7 y
	69, M	Oropharynx	Not reported	Polyclonal plasmacytic inflammatory infiltrate throughout the connective tissue.		Persistent disease, 10 y, recent flare
	53, F	Supraglottic, glottic larynx	Smoker for over 20 years		Stained polyclonal for κ and λ light chains; negative for gene rearrangement in Ig-encoding region. Warthin-Starry, GMS, Gramm stains were negative for microorganisms.	Persistent disease, 15 y

Table 1, we summarized all such cases published in English literature. The median age at presentation was 46 years old and ranging from 27 to 69 years old. We found that this age range is significantly less compared to short-term follow-up cases of MMP. It can be explained by quicker loss of follow-up in older population due to comorbidities. No deference was found in gender predilection in long-term vs short-term follow-up cases. The clinical course of MMP is typically waxing and waning with periods of long remissions. Progression to loss of organ functions in treatment-resistant cases is not uncommon. Histological representation of cases with long-term follow-up shows a few distinctive features that are discussed in greater details further. There is no consensus on the treatment for MMP; it includes steroids as first-line therapy and various topical or systemic immunosuppressive agents, i.e. tacrolimus, cyclosporin, methotrexate, chlorambucil, and dapsone [2,12,13]. Low-dose radiotherapy was also reported [1].

The etiological factors of MMP are still not clear, but role of exogenous factors was suggested based on possible association with smoking and long-term use of dentures [5]. On the other hand, a number of MMP patient with autoimmune or immune-mediated disease were observed suggesting a possible implication by the systemic processes [2,14]. Gross presentation of MMP shows significant variation and includes papillomatous, cobblestone, nodular, or granulomatous mucosa and sometimes hyperplastic proliferation of mucosa resulting in fungating ulcerated mass. The later can grossly mimic squamous cell carcinoma (SSC). Considering commonly found florid pseudo-epitheliomatous hyperplasia in overlying epithelium of MMP, serious caution should be taken when evaluating such cases. Only one case of MMP with associated invasive SSC was reported in an ex-smoker patient with a history of chemotherapy [11]. Other clinical differential diagnosis commonly includes lichen planus, lymphoproliferative disorders, infection, sarcoidosis, and granulomatosis with polyangiitis. Close histopathological examination is important to rule out most of these conditions. Rhinoscleroma can be considered in differential diagnosis since it can present with hyperplastic mucosa with inflammatory infiltrate with abundant plasma cells. However, vasculitis is commonly seen in rhinoscleroma, and foamy macrophages with gram negative bacteria, confirmed by special stains are diagnostic. Plasma cell gingivitis shows similar histological features, but it is a localized hypersensitivity reaction to offending agents, which typically resolves after their removal, thus confirming the diagnosis clinically [15].

Most diagnostic challenges of MMP arise from its histologic similarities with plasma cell neoplasm and lymphomas that can also manifest as dense infiltrate of plasmacytoid cells in the lamina propria. Thus, Ig clonality studies are warranted for appropriate diagnosis. Virtually all cases with long-standing history of MMP and treatment resistance develop significant changes in overlying epithelium including pseudo-epitheliomatous and/or psoriasiform changes. Interestingly, dyskeratosis in the absence of other Bowenoid features have been frequently reported. Secondary reactive changes in epithelium could be seen and include mixed inflammatory infiltrate,

polymorphonuclear leukocyte exocytosis and even intraepithelial microabscess formation. The plasma cells in MMP usually do not show atypical features such as prominent nucleoli or Dutcher bodies, but Russel bodies are not uncommon. Plasma cells stain positive for CD138 and CD38 without expression of aberrant markers such as CD56. It is reasonable to assess tissues for HHV8 since mixed inflammatory infiltrate enriched by polytypic plasma cells can be seen in Kaposi sarcoma. As noted before, it is important to assess polyclonal nature of plasma cell infiltrate by surface Ig immunochemical stains or in-situ hybridization. The most reliable study to evaluate clonality is Ig gene rearrangements by PCR. Only very few reported cases of MMP including ours were assessed by clonality studies. Interpretation of plasma cell clonality by Ig gene rearrangement can be challenging considering presence of non-specific pick(-s) in reactive polyclonal background especially in long-standing MMP. These cases should be reassessed by comparing sub-clones from previous biopsies.

To conclude, nearly all reported cases of CP have required multiple biopsies and numerous additional studies before a definitive diagnosis could be achieved. Clinicopathological correlation is crucial in confirming the diagnosis.

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