Oromandibular parafunction in chronic graft versus host disease: novel association and treatment approach

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Chronic graft-versus-host disease (cGVHD) affects 30-70% of patients following allogeneic hematopoietic stem cell transplantation (allo-HSCT), despite routine prophylactic treatment with potent immunosuppressants. This is an immune-mediated, multi-system disorder that can involve the skin, mouth, eyes, gastrointestinal tract, liver, lungs, genital tract and joints.

Neurological involvement in cGVHD is rare. We report five patients with a background of allo-HSCT complicated by cGVHD, who presented with parafunctional jaw clenching either in isolation, or in association with other involuntary muscle overactivity. We discuss potential mechanisms linking the conditions and our approach to treatment.
**Patient 1**: A 36-year-old man presented with a two-year history of jaw locking and trismus. This was associated with temporal pain and nocturnal bruxism. He had a background of longstanding severe cGVHD following allo-HSCT for the treatment of acute lymphoblastic leukemia 10 years prior. This affected his oral cavity, esophagus, eyes, lungs, and skin, and required long-term immunosuppression (prednisolone and cyclosporin). Examination revealed bilateral masseter hypertrophy, chronic ulceration of the buccal mucosa and limitation of mouth opening. Needle EMG of the right masseter was normal. He was treated with EMG-guided botulinum neurotoxin (onabotulinum toxin A; BOTOX®) into masseter (30U) and temporalis (15U) bilaterally with significant improvement in symptoms. He continues to receive 3-monthly injections with ongoing benefit.

**Patient 2**: A 56-year-old woman presented with a 1-year history of uncomfortable jaw clenching and trismus. She had a history of cGVHD with oral mucosal involvement and xerostomia, following allo-HSCT for the treatment of acute myeloid leukemia (AML) 14 years prior, no longer requiring immunosuppression. Twelve years prior to presentation she developed orofacial dyskinesia, choreoathetoid movements attributed to subcortical ischemia and which responded to long-term treatment with low dose risperidone. Examination revealed masseter hypertrophy, intermittent jaw clenching, platysma spasm and mild orobuccal dyskinesia. She was treated with EMG-guided botulinum neurotoxin (onabotulinum toxin A; BOTOX®) into each masseter (25U) and platysma (10U), with significant improvement in symptoms. She continues to require 3-monthly injections with a sustained treatment response.

**Patient 3**: A 58-year-old man presented with jaw pain, clenching and nocturnal bruxism 3 years after allo-HSCT for treatment of myelofibrosis. There were also intermittent painful spasms of the thighs, calves and forearms. He had severe restrictive lung disease secondary to pulmonary cGVHD requiring extracorporeal photopheresis (ECP) and mild oral, gut, and ocular involvement. Examination revealed masseter hypertrophy, intermittent involuntary jaw clenching and restricted mouth opening. He was treated with EMG guided botulinum neurotoxin (onabotulinum toxin A;
BOTOX®) into bilateral temporalis (10U), masseter (15U), and medial pterygoid (15U) with significant improvement. One year later he developed muscle pain and tightness in his neck and shoulders, and painful right facial spasms involving the cheek and eye. Additional injections were given into platysma and right lower pre-septal orbicularis oculi. Repeat injections continue at 3-monthly intervals, with sustained benefit over 5 years of follow-up, although increasing doses of neurotoxin have been required.

Patient 4: A 52-year-old woman presented with symptoms of jaw locking while eating and talking, nocturnal grinding and jaw pain 6 years post allo-HSCT for treatment of myelodysplasia. She had cGVHD involving the oral cavity, liver, gut and skin, requiring long term prednisolone. Examination revealed marked restriction of mouth opening without facial or jaw weakness. She was treated with botulinum neurotoxin (onabotulinum toxin A; BOTOX®) into bilateral masseters (20U), temporalis (10U) and medial pterygoids (15U), with significant benefit. She experienced the side effect of transient dysphagia attributed to the medial pterygoid injections, subsequently omitted. She continues to have sustained benefit from 4-monthly injections, over 6 years of follow-up.

Patient 5: A 27-year-old man presented with an 18-month history of bruxism and trismus with superimposed painful masseter spasms and painful spasms of long finger flexors in the forearms. He had severe cGVHD complicating allo-HSCT 3 years prior for treatment of AML. cGVHD caused chronic xerostomia, severe sclerodermatous changes in the skin, joint contractures, retroperitoneal fibrosis, chronic dry eyes and cataracts. He was treated with long-term prednisolone and ruxolitinib. Examination revealed restricted mouth opening and masseter hypertrophy bilaterally. MRI of the painful forearm muscles demonstrated normal muscle signal, with no features of muscle inflammation or fibrosis. Treatment with botulinum neurotoxin injections was declined.

Discussion:
Neurological involvement in cGVHD is rare, however immune-mediated central nervous system involvement (including encephalitis, demyelination and angiitis), and peripheral nervous system
disorders (including myositis, demyelinating neuropathies and myasthenia gravis) have been described. To our knowledge, this is the first description of parafunctional jaw clenching in patients with cGVHD; clinical features are summarized in Table 1. Furthermore, there have been no descriptions of painful muscle overactivity in other regions. Three of the 5 cases described here had more widespread painful muscle overactivity: case 5 (painful cramping in the forearms), case 3 (cramping in the forearms, thighs and calves, and pain in the neck and shoulders), and case 2 (involuntary movements in all four limbs). Two patients had involuntary hyperkinetic movements in the craniocervical region (Patients 2 and 3).

“Parafunctional jaw overactivity” refers to jaw bracing, tooth clenching and grinding due to overactivity of the physiological action of the stomatognathic system, however the underlying pathophysiology varies depending on the context.

We considered the possibility of myositis causing these symptoms. Chronic myositis is a well-described manifestation of cGVHD, however usually presents with symmetrical limb girdle and neck flexion weakness, not seen in these cases. Further arguing against this, creatine kinase elevation is present in the vast majority of described cases (normal in patients 1 and 4), diagnostic needle EMG of the overactive masseters was normal in case 1, and MRI of symptomatic forearm muscles was normal in case 5.

Given the high prevalence of parafunctional jaw overactivity in the general population the possibility of chance co-occurrence requires consideration. Several observations argue against this. Firstly, the patients described here had significantly more severe pain and trismus when compared to those treated at our center with otherwise similar symptoms. In addition, the course of botulinum toxin therapy has been notably prolonged; none have had remission of their symptoms and most have required increasing doses of botulinum toxin to alleviate jaw clenching. Secondly, there is painful muscle overactivity in other skeletal muscle in 3 of the 5 cases described. Thirdly, case 3 manifested dystonic muscle overactivity in the form of involuntary repetitive jaw clenching at rest,
and overflow with blepharospasm, dystonic overactivity of the platysma, and associated neck and shoulder pain. Case 2 had prior exposure to neuroleptic medications, therefore her symptoms may arguably represent the well-characterized entity of tardive dyskinesia/bruxism. However, we decided to include this case in our series due to other fundamental similarities.

We propose that the jaw muscle overactivity in these cases may represent a focal dystonia. The delay of several years (range 1.5-13 years) between the development of cGVHD and the onset of symptoms in these cases, while not specific for, would be in keeping with the development of acquired dystonia. Abnormal patterns of movement are thought to occur in some acquired dystonias due to maladaptive changes in the cortical circuits and altered sensorimotor processing resulting from altered afferent input. GVHD often results in marked mucosal, salivary gland and dental damage, and sclerodermatous restriction of skin and mucosal tissue can restrict mouth opening. All patients described here had oral symptoms from cGVHD. It is possible that alterations in sensory input due to chronic oral inflammation result in altered sensorimotor processing, and the development of an acquired focal dystonia in the form of involuntary jaw clenching.

Psychosocial factors may contribute to some parafunctional jaw symptoms. It has been recently described that in otherwise healthy adults, sleep bruxism is associated with higher salivary cortisol levels and higher levels of perceived anxiety or stress. Routine screening for psychosocial distress identifies nearly half of those treated with HSCT have symptoms of depression, anxiety or post-traumatic stress disorder. Later, HSCT survivors frequently suffer ongoing distress due to intrusive recollections of noxious treatments, treatment side effects, and fear of relapse, among many other contributors. Furthermore, allo-HSCT recipients (especially with significant cGVHD) have uniformly had high levels of corticosteroid exposure over a long period, however, there is no evidence to suggest a relationship between exogenous corticosteroids and bruxism to date.

Treatment options for cGVHD with oral involvement include systemic immunosuppression, topical steroids and artificial saliva. For trismus, physical therapy and passive stretching has been
suggested.\textsuperscript{10} Based on our observations, involuntary muscle overactivity may be contributing to symptoms in other patients with cGVHD and botulinum toxin may be of benefit. We have observed significant benefit with low incidence of side-effects following injections to the masseter (20-30U), temporalis (15-20U) and medial pterygoid muscles (15-25U) with doses titrated to response.

In summary, we have described five cases of parafunctional jaw overactivity in the context of cGVHD. The aetiology of this is uncertain and warrants further exploration. The association between the two conditions may be under-recognized and patients with cGVHD presenting with trismus should be evaluated for bruxism and other patterns of jaw muscle overactivity. Targeted botulinum toxin injections may be of therapeutic benefit in selected cases.

References:

4. Ilana Schlam, Samantha Buszek*, James Essell; Myositis-like Chronic Graft Versus Host Disease: Case Series and Literature Review. \textit{Blood} 2017; 130 (Supplement 1): 5508.


## Table 1: Summary of Clinical Features and Treatment

<table>
<thead>
<tr>
<th></th>
<th>Awake or sleep bruxism</th>
<th>Limitation of mouth opening</th>
<th>Jaw locking</th>
<th>Headache, TMJ, or facial pain</th>
<th>Extra-mandibular muscle overactivity</th>
<th>Masseter hypertrophy</th>
<th>Latency between cGVHD features and oromandibular parafunction (years)</th>
<th>Treatment</th>
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</table>
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ABSTRACT:
Chronic graft versus host disease (cGVHD) complicating allogeneic hematopoietic stem cell transplantation rarely involves the nervous system; oromandibular parafunction has not been previously reported. We describe five patients with cGVHD, presenting with bruxism, limitation of mouth opening, jaw locking, pain, and masseter hypertrophy. Pathophysiologic mechanisms are discussed. Targeted botulinum toxin injections were an effective treatment with minimal side effects.

Key Words: mandibular dystonia, parafunction, bruxism, graft versus host disease
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