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Adult-onset asthma and periocular xanthogranuloma – A rare infiltrative disease of the orbit and eyelid

Michael B. Green [a,b], Mary K. Daly [a,b,c], Nora M.V. Laver [d], Daniel R. Lefebvre [a,c,*]

[a] Veterans Affairs Boston Healthcare System, Department of Ophthalmology, 150 South Huntington Avenue, Boston, MA, 02130, USA
[b] Boston University School of Medicine, Department of Ophthalmology, 72 East Concord Street, Boston, MA, 02118, USA
[c] Harvard Medical School, Department of Ophthalmology, 243 Charles Street, Boston, MA, 02114, USA
[d] Tufts University School of Medicine, Department of Ophthalmology and Department of Pathology and Laboratory Medicine, 800 Washington Street, Boston, MA, 02111, USA

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ABSTRACT

Purpose: To present a case of adult onset asthma with periocular xanthogranuloma (AAPOX), and discuss existing literature on adult orbital xanthogranulomatous diseases (AOXGDs) and their treatment.
Observations: A 63 year old male presented with progressive bilateral eyelid swelling with overlying yellow plaques associated with asthma. CT scan showed periorbital swelling with enlargement of the superior and lateral rectus muscles bilaterally. Biopsy demonstrated orbital xanthogranulomatous disease with increased IgG4 plasma cells. The patient was treated with intralesional triamcinolone, oral prednisone, and cyclophosphamide without significant improvement. Surgical debulking was eventually performed which improved his external symptoms until he was lost to follow up 15 months later.
Conclusions and Importance: AOXGDs are a group of rare infiltrative diseases of the eyelids and orbit that can be associated with significant systemic morbidities. While they all have similar underlying histopathologic features, appreciating the clinical difference between these diseases is important in understanding patient prognosis and ensuring appropriate clinical monitoring. There is also growing research demonstrating that AAPOX, along with other AOXGDs, may represent part of a continuum of IgG4 related disease, similar to what is seen in this case. There is currently no reliably effective treatment for AOXGDs, and additional research into the management of these diseases is necessary.

1. Introduction

Adult orbital xanthogranulomatous diseases (AOXGDs) are a group of rare non-Langerhans cell histiocytoses characterized by xanthogranulomatous infiltration of periorbital and orbital tissues. The existing literature divides AOXGDs into 4 different syndromes: adult onset xanthogranuloma (AOX), adult onset asthma with periocular xanthogranuloma (AAPOX), Erdheim-Chester disease (ECD), and necrobiotic xanthogranuloma (NBX). These diseases share similar histological patterns but differ in their systemic associations and overall prognosis. Because of the rarity of these diseases, effective treatment is poorly understood. Here we present a case of AAPOX and discuss the existing literature relating to the treatment of this disease as well as an increasingly studied association with an autoimmune disorder known as IgG4-related disease.

2. Case report

A 63-year-old man with a past ocular history of dry eye and color-blindness bilaterally presented to the oculoplastic clinic for evaluation of prolapsed orbital fat and bilateral ptosis worse on the right. His symptoms had been worsening over the course of a year with decreasing vision on the right due to ptosis; he denied pain, diplopia, or changes in vision. The patient's medical history was significant for hypertension, type 2 diabetes mellitus with possible diabetic papillopathy of the left eye, hyperlipidemia, COPD, and asthma (age of onset not recorded). At initial presentation, visual acuity was 20/20 in both eyes with no afferent pupillary defect. Intraocular pressures were 19 mmHg and 20 mmHg in the right and left eyes respectively and increased to 25 mmHg and 24 mmHg respectively on upgaze. On periocular examination he was found to have edema of the right upper and lower lids with a

* Corresponding author. Veterans Affairs Boston Healthcare System, Department of Ophthalmology, 150 South Huntington Ave. Boston, MA, 02130, USA.
E-mail address: daniel.lefebvre@va.gov (D.R. Lefebvre).

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heterogeneously firm yellow plaque resembling a xanthelasma (Fig. 1). There was bilateral ptosis with a margin reflex distance 1 of −0.5 mm on the right and 2.5 mm on the left. Palpebral fissures were 5 mm on the right and 8 mm on the left. Levator function was 14 mm and 15 mm on the right and left eyes respectively. Hertel's exophthalmometer measured 23 mm on the right and 25 mm on the left. Anterior segment slit lamp exam was unremarkable.

Thyroid studies including thyroid stimulating hormone (TSH), T3, free T4, thyroid peroxidase (TPO) antibody, thyrotropin-binding inhibitory immunoglobulin (TBII), and thyroid stimulating immunoglobulin (TSI) were all normal. A CT scan with contrast revealed prominent periorbital pre-septal enhancing soft tissue bilaterally, right greater than left, extending into the post-septal space with enlargement of the superior rectus/levator complex and lateral rectus muscles bilaterally (Fig. 2A and B). The normal thyroid studies along with physical examination and imaging findings that demonstrated the presence of abnormal tissue infiltration from the skin through the orbital septum into the orbit informed a differential diagnosis that included idiopathic orbital inflammatory disease, IgG4-RD, Kimura disease, amyloidosis, sarcoidosis, AOXGDs, Langerhans cell histiocytosis, Rosai-Dorfman disease, granulomatosis with polyangiitis, or neoplasm including lymphoproliferation or other malignancy. A biopsy was therefore performed of the right upper eyelid and anterior orbit, which revealed xanthogranulomatous infiltration through skeletal muscle fibers, perivascular, and perineural soft tissues (Fig. 3A and B). The infiltrative cells were predominantly lipid laden histiocytes (CD68 immunohistochemical stain positive), lymphocytes, fibroblasts, scattered eosinophils, and few foreign body giant cells. There was a dense reactive lymphoplasmacytic (strong $CD3^{+}$, sparse $CD20^{+}$) infiltration with a polytypic population of plasma cells present; in situ hybridization for kappa and lambda stains showed a mixture of plasma cells with normal ratios (Fig. 4A). Alcian blue and mucicarmine stains were negative. IgG and IgG4 stains showed an increased number of IgG4 staining plasma cells present with an IgG4/IgG ratio of 0.5 (Fig. 4B).

Based on the patient's clinical and histological features, a diagnosis of adult onset asthma with periocular xanthogranuloma was made. The patient was started on a course of oral prednisone 80 mg taper but was transitioned to a 45 day course of 150 mg cyclophosphamide daily due to symptom recurrence with cessation of steroids. The patient was also treated with five triamcinolone intralesional injections in the right upper and lower lids as well as 3 injections in the left lower lid. Despite medical treatment, the patient's lid swelling only improved mildly and he continued to experience ptosis and visual obstruction. After approximately 4 years, bilateral orbitotomy with debulking was performed which lead to symptomatic improvement. The patient was last seen 15 months after surgical treatment and showed stable improvement of lid aperture at that time and was symptomatically doing well. The patient was subsequently lost to follow up.

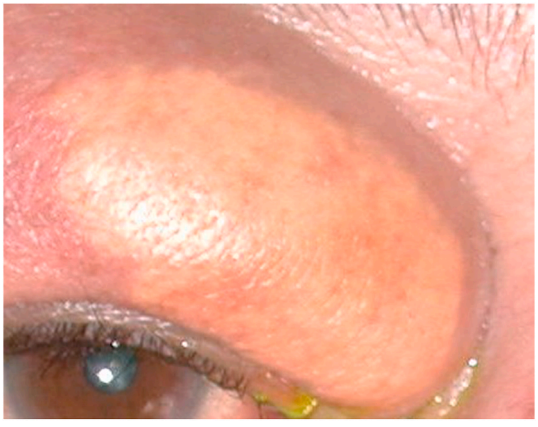

Fig. 1. External picture of the right upper eyelid fullness and ptosis with a prominent firm yellow lesion medially. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Langerhans cell histiocytosis is a disorder characterized by the proliferation of dendritic cells with CD1a and S-100 positivity by immunohistochemistry and Birbeck granules seen by electron microscopy. In contrast, Non-Langerhans cell histiocytoses (or class II histiocytoses) are a diverse group of benign and malignant disorders of monocyte/macrophage cell proliferation characterized by the absence of Langerhans cells. Adult orbital xanthogranulomatous diseases (AOXGDs) are a rare subgroup of non-Langerhan cell histiocytoses that present with subcutaneous, subconjunctival, and periocular locally invasive xanthogranulomatous inflammatory lesions.[1] Eyelid lesions associated with these disorders can look similar to xanthelasmas but are more indurated and extend into deeper orbital tissues. These conditions are further classified into 4 syndromes based on their associated systemic manifestations: adult onset xanthogranuloma (AOX), adult onset asthma with periocular xanthogranuloma (AAPOX), Erdheim-Chester disease (ECD), and necrobiotic xanthogranuloma (NBX). Differentiating between these conditions clinically is necessary for disease prognostication.

These four entities share common histological patterns: sheets of mononuclear xanthoma cells (foamy histiocytes), Touton giant cells, and variable lymphoid infiltration. On immunohistochemistry, these foamy histiocytes typically express CD68, CD163, and factor XIIa, but lack CD21, CD35, S100, CD1a, and Birkbeck granules.[2] Lymphocytes are seen in two general patterns: lymphoid aggregates with typical B cell-containing germinal centers (most common in AAPOX) and diffuse lymphocytic infiltrate ($CD8^{+}$ T cell predominate) admixed with proliferating fibroblasts (most common in ECD). In addition to these common features, cases of NBX also show characteristic geographic necrotic areas surrounded by a palisade of epithelioid histiocytes.[1] Interstitial mucin deposits, which stain with Alcian blue and mucicarmine stains, are usually present and are useful in differentiating from other pathologies.

Because these diseases share similar histological features, clinical characteristics and systemic associations are critical to appropriate diagnosis and management. AOX is the rarest of these four entities and is characterized by isolated pre-septal, and anterior orbital lesions that can sometimes be self-limited.[1] ECD is the most dangerous and most clinically dissimilar of the four AOXGDs. While ECD does not commonly present with ocular symptoms, it can present with xanthogranulomatous eyelid lesions.[3,4] Importantly, it is unique among the AOXGDs in that orbital manifestations are often intraconal and can include diffuse, apical, or even intracranial tissue infiltration.[1] This posterior orbital involvement is significant and puts patients at risk for exophthalmos and compressive optic neuropathy leading to blindness.[4] Furthermore, ECD is complicated by substantial morbidity due to associated long bone osteosclerosis, central diabetes insipidus, retroperitoneal infiltration causing possible renal dysfunction, cardiac involvement, and interstitial lung disease.[5]

NBX is the most frequently reported AOXGD.1 Clinically, it presents with yellow-orange or reddish-brown indurated nodules and plaques that, over time, can begin to ulcerate and fibrose leading to local tissue destruction.[6] These lesions are most frequently seen in the periorbital region and anterior orbit (60–80%), but can involve multiple sites including the trunk, face, arms, and legs.[1,6] This condition is highly associated with the development of paraproteinemia (80% of patients) as well as multiple myeloma, B-cell lymphoma, chronic lymphocytic leukemia, and other lymphoproliferative disorders.[6] Because of the risk of hematologic dyscrasia, it is important for clinicians to consider regular surveillance of complete blood counts, inflammatory markers, and serum protein electrophoresis in these patients.

The final AOXGD subtype, as seen in the case presented here, is AAPOX. As the name suggests, the defining feature of this condition is its

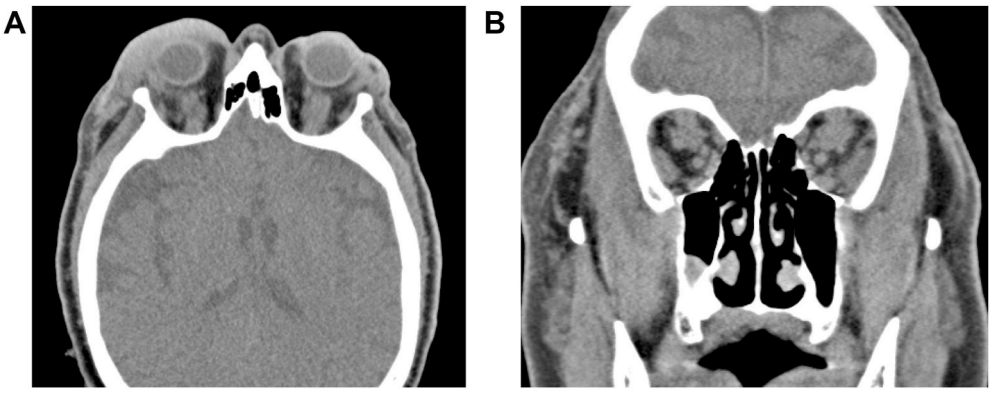

Fig. 2. A) Axial CT scan of orbits with contrast demonstrating enhancing soft tissue throughout the right upper eyelid area. B) The coronal reconstruction demonstrates enlargement of the extraocular muscles of the bilateral orbits (lateral recti and superior rectus/levator complex) likely representing extraocular muscle xanthogranuloma infiltration.

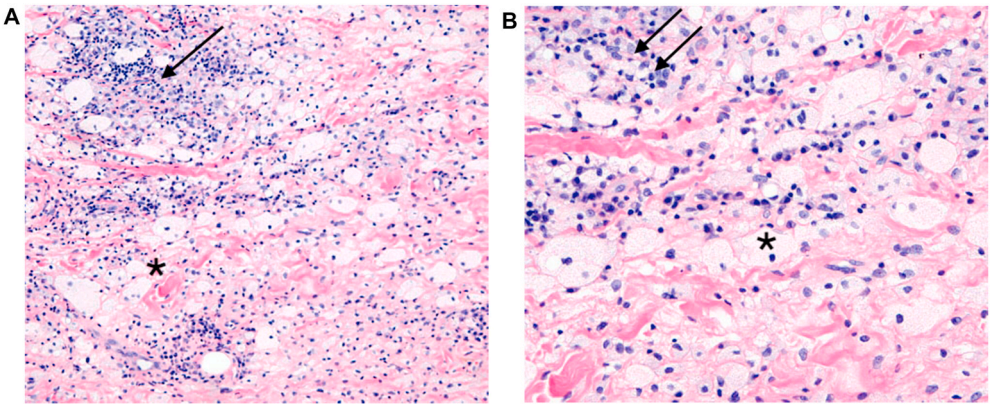

Fig. 3. A) Orbital soft tissues infiltrated by lipid-laden macrophages (asterisk), lymphocytes, and plasma cells (arrow) (H&E, x10). B) Higher magnification of lipid-laden macrophages (asterisk) and lymphocytes (arrow) (H&E, x20).

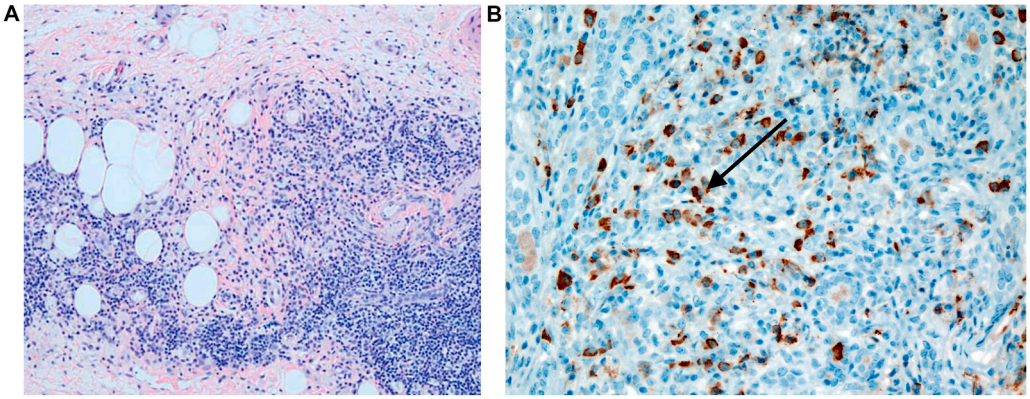

Fig. 4. A) Dense lymphoplasmacytic infiltration (H&E, x4). B) Increased population of IgG4 plasma cells (brown stain, arrow) by immunohistochemistry (IgG4 immunohistochemical stain, x20). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

association with adult-onset asthma. In most cases, patients develop mild to severe asthma within months to years following periocular symptom onset,[7,8] having been shown to precede orbital symptoms by up to 7–9 years.[8,9] AAPOX lesions often extend into the anterior orbital fat and have been shown to occasionally infiltrate the lacrimal glands and extraocular muscles leading to dry eye[7] and diplopia.[8,10] There is a well-documented association between AAPOX and chronic rhinosinusitis, nasal polyps, elevated serum IgE, and eosinophil infiltration of affected periorbital tissue.[1,7,8,11,12] While its pathogenesis is still poorly elucidated, a possible atopic etiology of this disease has been proposed.[8] Additionally, AAPOX is frequently associated with elevated serum polyclonal IgG, benign reactive lymphadenopathy, paraproteinemia, and rarely other lymphoproliferative disorders which may imply B-cell involvement in disease pathogenesis.[1,2,13,14]

Interestingly, the association between AAPOX and IgG4-related disease (IgG4-RD) is becoming more frequently examined. IgG4-RD is a systemic fibrosing autoimmune disorder associated with raised serum IgG4 levels and histological IgG4-positive plasma cell infiltration. It has

been shown to cause a wide range of systemic diseases including autoimmune pancreatitis, sclerosing cholangitis, and retroperitoneal fibrosis, among others.[15] It can also cause ophthalmic disease such as chronic lid swelling, orbital inflammatory disease (dacryoadenitis, orbital myositis), scleritis, and nasolacrimal duct obstruction.[15–18] Like AAPOX, IgG4-RD shows associations with atopic manifestation in addition to elevated IgG levels and lymphadenopathy.[9,19,20] FDG PET/CT imaging in AAPOX patients have also shown increased uptake in areas commonly effected by IgG4-RD (lacrimal glands, lymph nodes, and peri-rectal fat).[13] At least 15 cases of AAPOX associated with elevated IgG4 have been reported with 5 of these patients having had a history of autoimmune pancreatitis.[9,11,12,14,18] IgG4 positive plasma cells have been present on orbital biopsies in many patients with AOXGD including those with AAPOX,[9,21,22] but it is debated whether these cases represent a continuum between these diseases or just nonspecific immunologic reactions in response to xanthogranulomatous infiltration.[21] A recent study by McKelvie et al.[23] demonstrated that eyelid involvement in systemic IgG4-RD was rare and that while some AOXGD cases showed IgG4 levels meeting criteria for IgG4-RD, they were significantly lower than in patients with true IgG4-RD. Similarly, it is unclear if our case represents IgG4-RD as it does fulfill criteria for probable disease set by Umehara et al.[24] but not by those of the Boston Consensus Criteria (Fig. 5).[25]

Because of the rarity of these diseases, there have been no randomized control trials studying treatment and recommendations are limited to evidence from existing case reports.

Systemic steroids have also been shown to be somewhat effective in the treatment of AAPOX. While there are reports of sustained regression with low dose steroid treatment,[13,26] there are many cases of disease recurrence with cessation of oral steroids.[7,11,18,27,28] Because of the numerous reports of treatment failure with oral steroids, including in our patient, it is likely that long-term low dose steroid therapy may be necessary to maintain disease remission for some patients. These doses have been shown to be associated with only minimal systemic adverse effects.[29]

Many case studies have also described promising treatment results with antimetabolite agents and other immune modulators. Maintenance low dose methotrexate and azathioprine in particular have been used often in conjunction with oral steroid tapers to successfully achieve disease remission in AOXGDs including AAPOX.[3,6,8,10,12,26] The addition of other immunosuppressive agents, such as cyclophosphamide and cyclosporin, have also shown efficacy in patients with this disease,[1,30]

Comprehensive diagnostic criteria for IgG4-related disease[i]

(1). Clinical examination showing diffuse/localized swelling or masses in single or multiple organs
(2). Hematological examination showing elevated serum IgG4 concentrations (>135 mg/dl)
(3). Histopathologic examination shows:
  a). Marked lymphocyte and plasma cell infiltration and fibrosis.
  b). Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40%
  and >10 IgG4+ plasma cells/HPF

Definite: (1) + (2) + (3)
Probable: (1) + (3)
Possible: (1) + (2)

[i] Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Modern rheumatology. 2012 Feb 1;22(1):21-30.

Boston criteria for the diagnosis of IgG4-related disease[ii]

Characteristic histological features of IgG4-related disease:
  a. Dense lymphoplasmacytic infiltrate
  b. Fibrosis, usually storiform in character
  c. Obliterative phlebitis

1) Specimens histologically highly suggestive of IgG4-related disease require all of the following:
  a. ≥ 2 characteristic histologic features (exception: lacrimal gland specimen requires only ≥1 feature).
  b. A minimum IgG4+ plasma cell count which varies by the organ involved (range 10 to 200 cells/hpf).
  c. An elevated IgG4+/IgG+ cell ratio of >40% (exception: aortic specimen requires a ratio of >50%).
2) Specimens with probable histological features of IgG4-related disease require all of the following:
  a. A single characteristic histological feature
  b. A minimum IgG4+ plasma cell count which varies by the organ involved (range 10 to 200 cells/hpf).

[ii] Deshpande V, Zen Y, Chan JK, Eunhee EY, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC. Consensus statement on the pathology of IgG4-related disease. Modern Pathology. 2012 Sep;25(9):1181-92.

Fig. 5. Two previously proposed criteria for the diagnosis of IgG4-related disease.

and it has been suggested that their respective B cell and T cell suppressive effects could be used to tailor treatments based on histopathological lymphocyte characteristics.[1] Rituximab has also shown to have a durable response in patients with AAPOX due to the likely B cell driven pathogenesis[14,31,32] though it remains unclear whether histological evidence of strongly positive $CD20^{+}$ lymphocytes is necessary for successful treatment.

Intralesional corticosteroid treatment for periorbital xanthogranulomas has been shown to be effective in some patients.[28,33] A study by Elner et al.[28] showed that periocular triamcinolone injection alone led to improvement in lid lesions as well as some cases of diplopia in AOX and NBX. However, it has also proven to be ineffective for substantial symptom control in other patients, similar to what was seen in our case.[33,34] There seems to be a paucity of reports related to AAPOX specifically, though its efficacy is likely to show mix results.

Surgical debulking can be a reasonable treatment in patients with visual axis obstruction or discomfort who have shown inadequate improvement with initial medical treatment alone.[1] However, surgical treatment does not treat the underlying disease process, and symptoms have been shown to frequently recur anywhere from 6 months to up to 9 years later.[7,33] Finally, radiotherapy has also been used, mostly as an adjunctive treatment, in patients with AOXGDs. It has shown some variable yet promising results in patients with NBX and ECD,[6,35] but reports are very limited for AAPOX and AOX specifically and show mixed results.[1,27,36]

In the case of our patient, his disease failed to show significant improvement with intralesional steroid injections, systemic steroids, and cyclophosphamide, ultimately requiring surgical debulking to finally relieve his visual obstruction symptoms. Unfortunately, our patient was lost to follow up one year after his surgical procedure, and as such the progression of his disease subsequently is unknown. Reasonable next steps in his treatment, had his disease recurred, would likely have included a trial of methotrexate, azathioprine, or even rituximab.

4. Conclusions

AOXGDs are a group of rare infiltrative diseases of the eyelids that can be associated with significant systemic morbidities. While they all have similar underlying histopathologic features, clinical difference between these diseases is important for patient prognosis and ensuring appropriate clinical monitoring. Our patient, specifically, likely represents a case of AAPOX with possible overlapping features of IgG4-RD. The challenging treatment course our patient experienced parallels the variable treatment efficacy demonstrated in previously reported cases of AOXGDs and emphasizes the need for additional research into the treatment of these diseases.

Patient consent

Patient deceased; no next of kin or power of attorney found in medical record.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: MBG, DRL, NMVL, MKD.

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