Immunogammopathies are clonal plasma cell proliferative disorders characterized by deposition of light or heavy chain Ig fragments in tissues, leading to organ dysfunction.

Within this spectrum of diseases are multiple myeloma, Waldenstrom's macroglobulinemia, and benign monoclonal gammapathy, as well as light chain deposition disease.

Ocular manifestations of immunogammopathies have been described in a variety of ocular structures, including the conjunctiva, cornea, uvea, and retina.

INTRODUCTION

- Multiple myeloma is one of the most common primary malignancy of bone. Represents more than 40% of primary bone cancers.
- It is a plasma cell disorder.
  - Monoclonal neoplasms related to each other by virtue of their development from common progenitors in the B lymphocyte lineage.

Multiple Myeloma: Incidence and Epidemiology

- 1% of all malignancies
- 10% of hematological malignancies (2nd most common)
- 3-4 per 100,000 population
- 16,000 new cases/yr; 11,000 deaths/yr
- Median age: 65 ys, 3%<40 yrs
- M:F (2:1)
- More in Blacks
- Etiology: unknown
- Risk: radiation exposure
Etiology

- Chromosomal alterations identified:
  - 13q14 deletions
  - 17p13 deletions
  - 11q abnormalities
- Common translocations
  - t(11;14)(q13;q32) and t(4;14)(p16;q32)

Multiple myeloma: Symptoms

- Fatigue
- Back pain
- Increased infections
- Hypercalcemia
- Renal insufficiency
- Hyperviscosity
**Multiple Myeloma: Diagnosis**

- **Bone marrow** containing more than 10% plasma cells or a plasmacytoma, plus at least one of the following:
  1. A *monoclonal protein* in the **serum**, usually more than 30 g/L
  2. A *monoclonal protein* in the **urine** OR
  3. **Lytic bone lesions**

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**Bone Marrow Plasma Cells**

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J.M. Khan, V. McBain, C. Santiago, N. Lois. Bilateral 'vitelliform-like' macular lesions in a patient with multiple myeloma. *BMJ Case Rep* (2010) [http://dx.doi.org/10.1136/bcr.05.2010.3049](http://dx.doi.org/10.1136/bcr.05.2010.3049)
Bone marrow plasmacytosis

Rouleaux on peripheral smear
Serous macular detachments in association with immunogammopathies, though rare, have been described.

This serous macular detachments may be with or without subretinal precipitates or fundus signs of serum hyperviscosity in patient with multiple myeloma, Waldenstrom's macroglobulinemia, and with benign polyclonal gammopathy.

Specifically in multiple myeloma, deposits on the posterior surface of the neurosensory retina and in the subretinal space anterior to the retinal pigment epithelium (RPE).

Multimodal imaging

including
- fluorescein angiography
- fundus autofluorescence
- OCT.

Presentation
**Fundus photographs** show mild retinal pigment epithelium changes.

**Fundus autofluorescence** shows hyperautofluorescent macular lesions surrounded by a wider area of granular hypoautofluorescence, more prominent OS.


**Fluorescein angiography** shows generalized intraretinal leakage, disc leakage, and some microvascular abnormalities.
OCT at the level of these lesions shows a macular detachment with vitelliform deposition on the anterior surface of the RPE and the posterior surface of the neurosensory retina, more prominent OS and associated with intraretinal vacuole formation at the level of the outer nuclear layer OS.

Follow-up SD OCT shows complete resolution of the vitelliform detachments after induction chemotherapy.

Light chain deposition disease presenting with bilateral isolated acquired vitelliform lesions.

Fundus examination reveals bilateral peculiar subretinal lesions at the level of the RPE.

Fundus autofluorescence hyperautofluorescent, consistent with the appearance of acquired vitelliform lesions.

Horizontal foveal OCT scans reveal corresponding subretinal hyporeflective deposits anterior to the RPE OS and no abnormality OD.
3. a multiple myeloma presenting with multiple acquired vitelliform detachments involving the macula and midperiphery. Fundus photographs show multifocal areas of subretinal yellow deposits OU separate from the subretinal fluid. Fundus autofluorescence these deposits are hyperautofluorescent on and consistent with the appearance of acquired vitelliform lesions. OCT shows neurosensory detachments with subretinal deposits; these resolved after bone marrow transplant, with residual subretinal fibrosis OD.

4. Fundus photographs show pigment epithelial detachments OU. Fundus autofluorescence with hyperautofluorescent material on more prominent OD. OCT shows pigment epithelial detachments OU with an overlying subretinal hyperreflective deposit OD resembling an acquired vitelliform lesion. Follow-up OCT shows resolution of the pigment epithelial detachments corresponding with a reduction in the multiple myeloma Ig numbers.
Prognosis

- Chronicity of the lesion (>6 months)
- Despite the presence of serous macular detachments in , the visual prognosis is usually good and With resolution of the acquired vitelliform detachments, we observed restoration of the normal outer retina and RPE anatomy on SD OCT except if detachments is associated with choroidal neovascularization, macular scar or macular hole formation.

Mechanism of subretinal fluid

- The metabolic reabsorption of subretinal fluid is dependent upon 2 main mechanisms.
  - 1- active ionic transport across the RPE and
  - 2- passive passage of fluid driven by the oncotic pressure gradient (higher in the choroid).
- These are the 2 main mechanisms that permanently dehydrate the subretinal space.
- Igs are large proteins that cannot passively diffuse across the RPE, there is no specific active transporter of Igs at the level of the RPE. Igs increase the oncotic pressure of the subretinal space, inversing the oncotic pressure gradient across the RPE. Fluid can therefore accumulate in the subretinal space, driven by the reversed oncotic pressure gradient. The fluid accumulating in the subretinal space physically separates the RPE from the photoreceptors, impeding proper phagocytosis.
Mechanism of autofluorescence

Therefore, outer segments containing fluorophores shed and accumulate in the subretinal space, resulting in the hyperautofluorescent signal present on fundus autofluorescence.

DD of acquired vitelliform lesions

Multiple etiologies are associated with acquired vitelliform lesions, including:
- conventional drusen,
- subretinal drusenoid deposits,
- cuticular drusen,
- some retinal dystrophies,
- tractional maculopathies, and
- central serous chorioretinopathy.

Vitelliform deposits are usually hyperautofluorescent and more or less homogenous depending on their etiology.
Treatment

- Treatment of the macular edema with intravitreal anti-VEGF or PDT is not effective.
- Oral prednisone (PO) alone is not effective.
- Plasmapharesis can improve retinal hge or tortuosity due to hyperviscocity but not vitelliform macular lesion and neurosensory detachment.
- Multiple myloma treatment is effective in the form of chemotherapy with 2 - 5 cycles of Velcade, a mitogen-activated protein kinase enzyme inhibitor; Revlimid; and Cytoxin Combined with PO 1mg/ kg. (up to 2years treatment) or Bone marrow transplant.

Conclusions

- Patients with an immunogammopathy such as multiple myeloma or light chain deposition disease may develop serous elevations of the macula that classified as acquired vitelliform detachments using multimodal imaging.
- Clinicians should be aware that the presence of a vitelliform macular detachment, even without signs of hyperviscosity-related retinopathy, may be attributable to plasma cell dyscrasias.
- **Appropriate work up** including
  - **Ocular**, the funduscopic, fluorescein angiogram, OCT, and fundus autofluorescence
  - **Systemic serum protein electrophoresis** and **hematology consultation** should be considered in the management of patients with acquired vitelliform detachments of uncertain etiology.

Home message

- Not every fundus lesion is a local ocular disease
- Ophthalmologist can save the live of the patient