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Orbital Infiltration in a Patient with Waldenström Macroglobulinemia: Need for Multidisciplinary Approach and Comparison with the Literature

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Abstract. The use of specific inhibitory drugs of intracellular signalling pathways (such as Bruton-Kinase inhibitors) for the treatment of Waldenström's macroglobulinaemia (WM) is a recognised risk factor for *Aspergillus spp.* infections. The overlapping clinical manifestations of the two diseases may require the involvement of different medical specialities. We describe the clinical course of a patient with pulmonary and encephalic aspergillosis, with concomitant orbital infiltration, which represented a difficult diagnosis: the case required a multidisciplinary approach to define the ocular lesions and an in-depth study of the literature.

Keywords: Waldenström's Macroglobulinemia; Invasive Aspergillosis; Orbital Lymphoma; Bruton Kinase Inhibitors; Lacrimal Glands Lymphoma.

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Introduction. Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma (LPL) belonging to the category of Non-Hodgkin B Lymphomas (NHL) with an indolent course, characterized by monoclonal immunoglobulin M (IgM) protein hypersecretion.¹ The median age of diagnosis is 70 years,² and the disease is much more common in the white population.³ Patients with WM can develop systemic symptoms (fever, weight loss, night sweats), symptoms related to bone marrow infiltration (e.g., anemia, leukopenia, thrombocytopenia), lymphoid tissues involvement (e.g., lymphadenopathy, hepatosplenomegaly) and IgM monoclonal proteins (e.g., hyperviscosity, peripheral neuropathy, renal disturbances).¹ Recurrent infections may also occur due

to a relative decrease of other immunoglobulin classes or as a consequence of treatment-induced immunosuppression. Treatment is indicated in symptomatic patients, firstly with anti-CD20 agents (e.g., rituximab) and chemotherapy, with the possible use of drugs such as BTK (Bruton tyrosine kinase) – inhibitors (e.g., ibrutinib, acalabrutinib or zanubrutinib) or proteasome inhibitors (e.g. bortezomib).⁴

We briefly present a case description of a patient affected with WM and treated with multiple lines, including ibrutinib. The clinical history became particular after the occurrence of intraorbital lesions requiring the involvement of a multidisciplinary approach in order to establish a correct diagnosis and

treatment.

Case Presentation

Clinical history. The patient was a 71 years-old male, affected with symptomatic WM since 2000, previously treated with a CHOP-like chemotherapy followed by rituximab consolidation in 2001. In 2006 he received rituximab and chlorambucil for a first relapse; in 2011, for a second relapse, he underwent treatment with rituximab, fludarabine, and cyclophosphamide and in 2017 with rituximab and bendamustine for a subsequent recurrence. For chronic obstructive pulmonary disease (COPD) exacerbations, the patients experienced several hospitalizations since 2018 and started intravenous immunoglobulin support for secondary, symptomatic hypogammaglobulinemia. The patient was also receiving entecavir for chronic HBV infection. Due to the increase of IgM protein, the presence of anemia, and the emergence of abdominal lymphadenopathies, ibrutinib was started in June 2019: a complete bone marrow (BM) evaluation was performed before starting the treatment, showing 80% of clonal lymphoplasmacytic BM infiltration. Multiparameter flow cytometry demonstrated a characteristic WM phenotype: CD19+, CD22+, CD79b+, FMC7+, IgM+, monoclonal kappa (*k*) light chain surface expression. *MYD88* gene mutation was tested as well, resulting positive for *MYD88*^{L265P} mutation. A partial response was then obtained, with the resolution of anemia, lymphadenopathy reduction, and decreased IgM monoclonal protein. In October 2020, the patient was admitted for symptomatic COVID-19 pneumonia, treated with remdesivir with rapid improvement.

Diagnosis of invasive aspergillosis. In December 2020, invasive pulmonary aspergillosis (IA) was diagnosed, according to sputum samples positive for *Aspergillus flavus* and *A. fumigatus*, bronchoalveolar lavage (BAL) *Aspergillus spp.* positive polymerase chain reaction (PCR), BAL-sample's galactomannan optical density index of 1.71, and chest high-resolution CT findings consistent with the disease. Antifungal therapy with isavuconazole was started in January 2021, improving the pulmonary lesions. Considering the diagnosis, ibrutinib treatment was briefly interrupted and restarted at a lower dose, considering the pharmacological interaction with isavuconazole.

In March 2021, he was admitted to a peripheral hospital for an epileptic crisis. A brainstem contrast-enhanced (CE) magnetic resonance (MR) was performed, showing a 12 mm nodular lesion in the left parietal lobe, weakly enhanced in T1-weighted (T1W) sequences and hypointense in T2-weighted (T2W) sequences, with ring enhancement, and a similar 4 mm finding in the right lobe. Additionally, the patient experienced a likely ischemic stroke.

Ibrutinib was suspended for cerebral IA suspect, a lumbar puncture was executed (microbiological samples resulted in negatives), and a cerebral biopsy of the bigger lesion was performed after a month, with evidence of fungal hyphae and spores and positive *Aspergillus spp.* PCR, confirming the encephalic fungal localization.

Laboratoristic progression of Waldenström macroglobulinemia. In May 2021, he was admitted to our hospital for hepatic toxicity related to isavuconazole, and antifungal therapy was switched firstly to liposomal B amphotericin, then to voriconazole. Brain C.E. MR in May 2021 was substantially unchanged. In August 2021, the stability of the radiological brain picture and improving lung imaging were confirmed with an additional CT examination.

During the same period, considering the evidence of atypical lymphocytes in blood smear and the serum levels of IgM 29.4 g/L (normal values 0.4-2.3), BM biopsy (BMB) was performed, with evidence of lymphoid interstitial infiltrate of 70-80% of cellularity, plasmacytoid elements and monoclonal expression of *k* light chain and M heavy chain: considering the absence of symptoms related to WM and the concomitant IA, the patient did not start any treatment for WM.

Orbital infiltration - Initial work-up. In September 2021, the patient was admitted for fever. For the evidence of a slight lymphocytosis, a peripheral blood flow cytometry was performed and showed the presence of a mature B lymphocyte population (CD19+, CD22+, IgM+ CD23 -/+ and clonal expression of *k* light chain). During hospitalization, the patient complained of bilateral conjunctivitis: at the examination, bilateral nodules were palpable under the eyebrow arch without pain, vision deficit, diplopia, or corneal involvement. Orbit CT (**Figure 1**) evidenced bilateral increased lacrimal glands (20x10 mm). Several (> 10) small and hyperdense nodularities (from 2 to 15 mm) were detected bilaterally in the eyelid's soft tissues and intra- and extra-conical endo-orbital areas. Nodular lesions were confirmed with an orbit CE MR (**Figure 1**), iso/hypointense in T1W sequences, and hypointense in T2W, with contrast enhancement. Similar findings were described in both maxillary sinuses and ethmoidal lamina papyracea. The Serum IgM level was 46 g/L (normal value: 0.4-2.3).

Differential Diagnosis. Orbital masses in the adult can occur in a wide range of diseases, including infections (e.g., *Staphylococcus spp.*, *Mycobacterium tuberculosis*, *Aspergillus spp.*), inflammatory diseases (e.g., IgG4-related sclerosing disease, systemic amyloidosis), vascular lesions (e.g., venous and arteriovenous malformations), benign (e.g. schwannoma, neurofibroma) and malignant tumors (e.g., B-cell lymphoma, metastasis).⁵ Lacrimal gland lesions account

Figure 1. Orbit CT (a), T1-weighted magnetic resonance (b), contrast enhanced T1-weighted magnetic resonance (c), T2-weighted magnetic resonance (d) showing bilateral enlargement of lacrimal glands and intra-orbital nodules (October 2021).

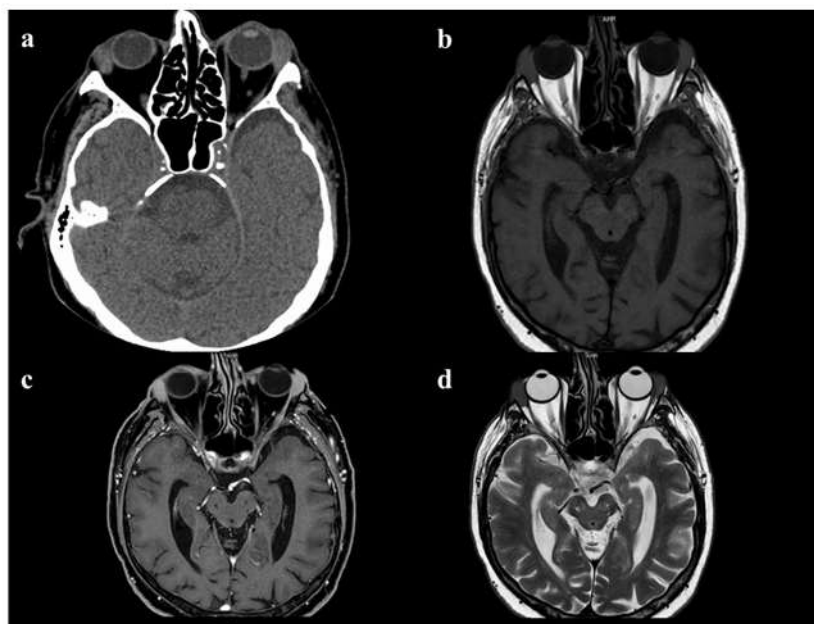


Table 1. Clinical, radiological and therapeutic differences between orbital involvement of Waldenström macroglobulinemia and invasive aspergillosis.

	Waldenström macroglobulinemia	Invasive Aspergillosis
Most common ocular manifestation	Retinal hyperviscosity syndrome	Endophthalmitis
Orbital manifestations	Bilateral masses	Unilateral mass, usually start from paranasal sinus
Lacrimal gland involvement	Rare, if present bilateral	Very rare, if present unilateral
Bone destruction	Very rare	Possible
Serum	Elevated IgM	Elevated Galactomannan
CT	Isodense	Calcifications (~ pathognomonic)
T1-Weighted MR	Iso-hypointense	Iso-hypointense, sometimes hypointense in the center
Contrast enhanced T1-Weighted MR	Homogeneous contrast enhancement	Homogeneous enhancement
T2-Weighted MR	Hypointense, lower intensity in the center	Hypointense, sometimes peripherally hyperintense
Treatment	Chemotherapy and/or Radiotherapy	Surgery and Antifungal therapy
Mortality	Not reported – in line with systemic disease, 13-64% dependently by prognostic group	Reported 50-86 %

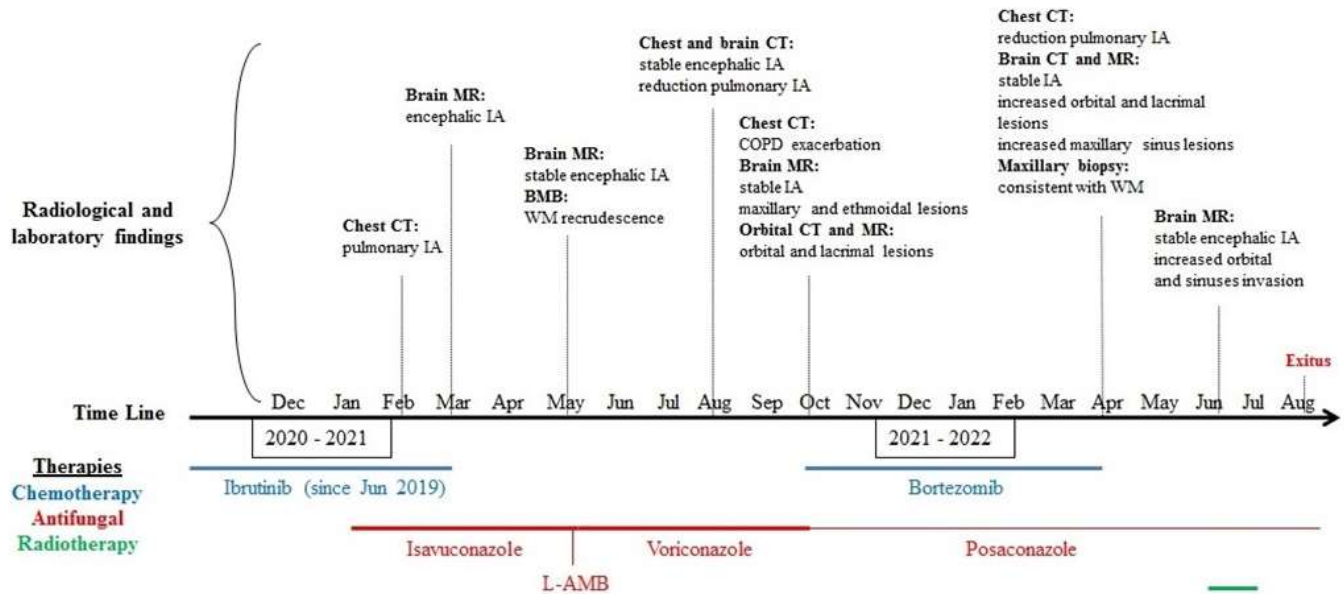
for approximately 10 % of all biopsied orbital masses: the most common causes are inflammatory (as IgG-4-related disease) or lymphoproliferative disorders, with potential bilateral involvement.^{6,7}

Considering the subacute onset of the manifestation (4 months since the last brain MR) and that intraorbital lesions are uncommon but possible in both IA and WM, we focused on the differential diagnosis between these two pathological entities. Orbital presentation's main differences are described in **Table 1**.

Further Examinations. Considering IA pulmonary picture improvement and encephalic lesions stability after eight months of antifungal therapy (**Figure 2**) and

the evidence of WM progression at BMB with peripheral blood involvement, after a multidisciplinary discussion, treatment with bortezomib (a proteasome inhibitor) was started in October 2021. At the same time, voriconazole was suspended, and the patient started posaconazole prophylaxis. According to ophthalmological and neuro-radiological evaluation, the patient was discharged with a scheduled clinical and radiological follow-up. He initially reported conjunctival chemosis reduction with decreased swelling, especially of the right eye. Five cycles of bortezomib were administered until February 2022. The patient was admitted in March 2022 for COPD exacerbation, presenting worsening bilateral orbital edema (**Figure 3**): decreasing pulmonary aspergillosis

Figure 2. Timeline of events from December 2020, evidencing radiological, histological and laboratory findings. Below the timeline are evidenced chemotherapy, antifungal therapy and radiotherapy.

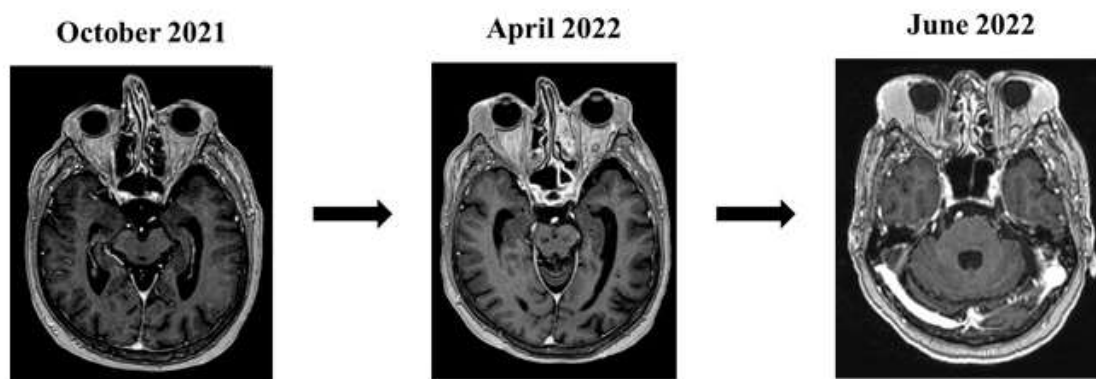


BMB: bone marrow biopsy; IA: invasive aspergillosis; L-AMB: liposomal B amphotericin; MR: magnetic resonance; WM: Waldenström macroglobulinemia

Figure 3. Evidence of bilateral orbital oedema and subcutaneous palpebral nodules at the clinical examination, April 2022.



Figure 4. Progression of lacrimal glands and intra-orbital nodules enlargement, contrast enhanced T1-weighted magnetic resonance, comparison between October 2021, April 2022 and June 2022.



lesions were confirmed at CT exam, in line with negative serum beta-D-glucan ad galactomannan, with no evidence of IA encephalic radiologic worsening. However, MR examination evidenced increased dimensions of known orbital lesions (Figure 4), with a worsening picture of erosive foci in subcutaneous,

maxillary, and ethmoidal areas, diffused also in left frontal and sphenoidal sinuses, mastoid and ethmoidal cells, bilaterally in nasal turbinates.

Final Diagnosis. Considering the worsening clinical picture, according to maxillofacial surgeons, palpebral

Table 2. Cases of Waldenström macroglobulinemia orbital involvement described in literature. Cases of orbital invasion in Bing-Neel syndrome, case reports written in French and Japanese languages were excluded.

Author	Year	Age, sex	Orbital involvement	Diagnostic confirmation	Serum IgM	Treatment	Infectious disease - differential diagnosis
Little [11]	1967	65, M	Bilateral lacrimal glands	HE	N.D	RdT	-
Schechterman <i>et al</i> [13]	1970	-	Bilateral lacrimal glands	-	-	ChT	-
Blatrix <i>et a.</i> [27]	1973	42, M	Not described (only symptoms)	-	-	-	-
Giarelli <i>et al</i> [32]	1982	60, M	Bilateral infiltrations of soft tissues	HE (post-mortem)	Elevated	ChT	N.D.
Moulis <i>et al</i> [33]	1989	52, F	Unilateral orbital mass	Not done	-	-	-
Lossos <i>et al</i> [34]	1990	75, M	Unilateral mass	Not done	-	-	-
Ettl <i>et al</i> [31]	1992	76, M	Unilateral orbital mass	FNAC	Elevated	RdT + ChT	N.D.
Krishnan <i>et al</i> [8]	1995	57, F	Bilateral lacrimal glands	HE	Elevated	ChT+ RdT	N.D.
Leone <i>et al</i> [14]	1996	74, F	Bilateral lacrimal glands + retinal involvement	FNAC	Elevated	ChT	N.D.
Kumar <i>et al</i> [25]	2005	32, F	Bilateral orbital mass	FNAC	Elevated	ChT	N.D.
Karimi <i>et al</i> [28]	2006	70, F	Bilateral orbital mass	FNAC	-	ChT	N.D.
Ranchod <i>et al</i> [24]	2008	77, M	Unilateral orbital mass	HE	Elevated	ChT + RdT	N.D.
Verdù <i>et al</i> [26]	2010	54, F	Bilateral orbital mass	FNAC	Elevated	N.D	N.D.
Hafezi <i>et al</i> [12]	2013	62, F	Bilateral lacrimal glands	-	-	ChT	-
Hellman <i>et al</i> [35]	2018	72, M	Infiltration of upper rectus muscle	HE	N.D.	N.D.	N.D.
Vangsted <i>et al</i> [9]	2020	63, M	Bilateral lacrimal glands	HE	Elevated	RdT	N.D.
Adiga <i>et al</i> [10]	2020	75, M	One orbital mass + bilateral lacrimal glands	HE	Elevated	ChT	N.D.
Guerin <i>et al</i> [15]	2022	74, F	Bilateral orbital lesions	HE	Elevated	ChT + RdT	N.D.
Our case	2022	71, M	Bilateral lacrimal glands + bilateral orbital lesions	HE	Elevated	ChT + RdT	Invasive Aspergillosis

ChT: chemotherapy; FNAC: fine needle aspiration cytology; HE: histological examination; N.D.: not described; RdT: radiotherapy; - : not available.

and maxillary biopsies were performed. The latter sample evidenced a picture consistent with LPL (lymphoid proliferation with plasma cells expressing IgM). Additional therapeutic cycles with bortezomib were not performed because of the increased infection risk and the progressively worsening performance status. IgM levels were reduced to 22.4 g/L (normal values 0.4-2.3).

Orbital infiltration was confirmed as a progressive WM involvement; interestingly, only eighteen cases in the literature from 1967 to nowadays report similar findings (Table 2). Lacrimal gland involvement is reported in only seven cases.⁸⁻¹⁴

In June 2022, intraorbital and maxillofacial diffusion worsened (Figure 4), involving nasal bones and extending to the left infratemporal fossa and alveolar processes through the ipsilateral maxillary sinus. Palliative radiotherapy was performed in June and July 2022. The patient experienced an additional COPD exacerbation needing hospitalization in July 2022 with concurrent pancytopenia (red blood cells $3.04 \times 10^{12}/L$, white blood cell $1.18 \times 10^9/L$, neutrophils $0.86 \times 10^9/L$, platelets $51 \times 10^9/L$). Serological markers of fungal

infection were persistently negative; an antimicrobial regimen and recombinant human granulocyte colony-stimulating factor (Filgrastim) were introduced. The patient was discharged after one week and died in August 2022

Discussion. The case denotes the diagnostic and therapeutic complexity of a patient affected by WM progression, a pathology requiring a multidisciplinary approach^{4,15,16} in the context of a pulmonary and encephalic IA.

Disseminate or extrapulmonary IA is commonly associated with hematopoietic cell/solid organ transplantation and hematologic malignant therapy:¹⁷ in particular, association with Bruton-kinase inhibitor (e.g., ibrutinib) is well described,¹⁸⁻²⁰ with encephalic involvement commonly reported.¹⁹

The most common *Aspergillus spp.* ocular manifestation is endophthalmitis, while the typical orbital aspergillosis is characterized by unilateral painful, red eye with proptosis,²¹ usually starting from paranasal sinuses.²² The involvement of lacrimal sack has been rarely described in the literature.²¹

In WM, the most common ocular manifestation (present in up to 34% of cases)²³ is hyperviscosity syndrome associated with fundoscopic abnormalities, characterized by characteristically tortuous "sausage link"-like retinal veins. Tumor infiltration of the orbital and periorbital tissues, involving retro-orbital lymphoid tissue and lacrimal glands, rarely occurs.²⁴ If it happens, it is described as bilateral masses,^{8,15,25,26} in some cases with palpebral edema,^{9,26} nodular palpebral involvement,¹⁰ and proptosis.²⁵ Bilateral swelling of lacrimal glands is an extremely rare presentation of WM and has been described only in a few cases in the literature,^{8–14,27} as well as bone involvement.²⁸ Orbital infiltration can be present also in Bing-Neel syndrome, a WM malignant form of the central nervous system, but usually with a more extended involvement.^{29,30} Radiologically, LPL lesions are usually mildly hypointense in T1W and T2W MR imaging,^{24,28,31} probably for the high density of tumor cells and low

interstitial water content.³¹ Lesions, shown in T1W sequences, are also characterized by homogeneous CE.^{24,28,31} Treatment for WM orbital involvement is not well defined, and in published case reports, chemotherapy alone^{10,14,28} or combined with local radiotherapy^{8,15,24} was used, with a reduction of symptoms, intraorbital masses, and blood IgM levels. In our case, although the reduction of IgM level (22.4 vs. 46 g/L), symptoms persisted, and orbital and maxillofacial foci gradually increased in size.

Conclusions. We reported a case of orbital WM with lacrimal glands involvement, rarely described in the available literature. Differential diagnosis between WM and IA was particularly difficult considering the two pathologies' systemic nature and overlapping clinical features. A correct diagnosis was reached only thanks to a multidisciplinary approach.

References:

- Mazzucchelli M, Frustaci AM, Deodato M, et al (2018) Waldenström's Macroglobulinemia: An Update. *Mediterr J Hematol Infect Dis* 10:e2018004. <https://doi.org/10.4084/MJHID.2018.004>
- Castillo JJ, Olszewski AJ, Kanath S, et al (2015) Overall survival and competing risks of death in patients with Waldenström macroglobulinaemia: an analysis of the Surveillance, Epidemiology and End Results database. *Br J Haematol* 169:81–89. <https://doi.org/10.1111/bjh.13264>
- Benjamin M, Reddy S, Brawley OW (2003) Myeloma and race: a review of the literature. *Cancer Metastasis Rev* 22:87–93. <https://doi.org/10.1023/a:1022268103136>
- Kastritis E, Leblond V, Dimopoulos MA, et al (2018) Waldenström's macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 29:iv41–iv50. <https://doi.org/10.1093/annonc/mdy146>
- Bs P, Mi V, A A, et al (2016) Orbital tumours and tumour-like lesions: exploring the armamentarium of multiparametric imaging. *Insights Imaging* 7. <https://doi.org/10.1007/s13244-015-0443-8>
- Kim JS, Liss J (2021) Masses of the Lacrimal Gland: Evaluation and Treatment. *J Neurol Surg Part B Skull Base* 82:100. <https://doi.org/10.1055/s-0040-1722700>
- Teo L, Seah LL, Choo CT, et al (2013) A survey of the histopathology of lacrimal gland lesions in a tertiary referral centre. *Orbit Amst Neth* 32:1–7. <https://doi.org/10.3109/01676830.2012.736595>
- Krishnan K, Adams PT (2009) Bilateral orbital tumors and lacrimal gland involvement in Waldenström's macroglobulinemia. *Eur J Haematol* 55:205–206. <https://doi.org/10.1111/j.1600-0609.1995.tb00253.x>
- Vangsted A, Mikkelsen LH, Jørgensen JS, Heegaard S (2020) Lymphoplasmacytic lymphoma infiltrating both lacrimal glands in a patient with Waldenström's macroglobulinemia. *Am J Ophthalmol Case Rep* 17:100597. <https://doi.org/10.1016/j.ajoc.2020.100597>
- Adiga S, Mehta A, Singh U, et al (2022) Waldenström Macroglobulinemia of the orbit: A diagnostic challenge. *Eur J Ophthalmol* 32:NP246–NP250. <https://doi.org/10.1177/1120672120963459>
- Little JM (1967) Waldenström's macroglobulinemia in the lacrimal gland. *Trans - Am Acad Ophthalmol Otolaryngol Am Acad Ophthalmol Otolaryngol* 71:875–879
- Hafezi F, Moesen I, Carels G, et al (2010) [Waldenström's macroglobulinaemia of the lacrimal gland in a patient with sarcoidosis]. *Ophthalmol Z Dtsch Ophthalmol Ges* 107:60–63. <https://doi.org/10.1007/s00347-009-2010-5>
- Schechterman L, Tyler SJ (1970) Waldenström's macroglobulinemia. Localization in ileum and lacrimal glands. *N Y State J Med* 70:2025–2029
- Leone G, Parisi V, Rebecchi A, et al (1996) Multiple ocular impairment in a patient affected by Waldenström's macroglobulinaemia. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol* 234:533–535. <https://doi.org/10.1007/BF00184864>
- Guerin C, Normile C, Quinn J, et al (2022) Orbital involvement in Waldenström macroglobulinaemia: a multidisciplinary approach. *Ir J Med Sci* 1971 - 191:2229–2230. <https://doi.org/10.1007/s11845-021-02846-2>
- Kapoor P, Ansell SM, Fonseca R, et al (2017) Diagnosis and Management of Waldenström Macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016. *JAMA Oncol* 3:1257–1265. <https://doi.org/10.1001/jamaoncol.2016.5763>
- Patterson TF, Thompson GR, Denning DW, et al (2016) Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 63:e1–e60. <https://doi.org/10.1093/cid/ciw326>
- Fürstenau M, Simon F, Cornely OA, et al (2020) Invasive Aspergillosis in Patients Treated With Ibrutinib. *HemaSphere* 4:e309. <https://doi.org/10.1097/HS9.0000000000000309>
- Ghez D, Calleja A, Protin C, et al (2018) Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. *Blood* 131:1955–1959. <https://doi.org/10.1182/blood-2017-11-818286>
- Maus MV, Lionakis MS (2020) Infections associated with the new "nibs and mabs" and cellular therapies. *Curr Opin Infect Dis* 33:281–289. <https://doi.org/10.1097/QCO.0000000000000656>
- Levin LA, Avery R, Shore JW, et al (1996) The spectrum of orbital aspergillosis: a clinicopathological review. *Surv Ophthalmol* 41:142–154. [https://doi.org/10.1016/s0039-6257\(96\)80004-x](https://doi.org/10.1016/s0039-6257(96)80004-x)
- Khoo SH, Denning DW (1994) Invasive aspergillosis in patients with AIDS. *Clin Infect Dis Off Publ Infect Dis Soc Am* 19 Suppl 1:S41–48. https://doi.org/10.1093/clinids/19.supplement_1.s41
- García-Sanz R, Montoto S, Torrequebrada A, et al (2001) Waldenström macroglobulinaemia: presenting features and outcome in a series with 217 cases. *Br J Haematol* 115:575–582. <https://doi.org/10.1046/j.1365-2141.2001.03144.x>
- Ranchod TM, Mansour TN, Fogt F, Gausas RE (2008) Waldenström macroglobulinemia of the orbit. *Ophthalm Plast Reconstr Surg* 24:76–77. <https://doi.org/10.1097/IOP.0b013e318160dfcc>
- Kumar S, Das S, Goyal JL, et al (2007) Bilateral orbital tumor formation and isolated facial palsy in Waldenström's macroglobulinemia. *Int Ophthalmol* 26:235–237. <https://doi.org/10.1007/s10792-007-9037-x>
- Verdú J, Andrés R, Sánchez-Majano JL, Fernández JA (2011) Bilateral ocular involvement as a presentation of Waldenström's macroglobulinemia. *Med Oncol Northwood Lond Engl* 28:1624–1625. <https://doi.org/10.1007/s12032-010-9648-3>
- Blatrix C, Fine JM, Yeme D, Lambin P (1973) [Tumoral forms of Waldenström's macroglobulinemia. Apropos of a case involving 2 localisations, orbital and hepatic]. *Sem Hopitaux Organe Fonde Par Assoc Enseign Med Hopitaux Paris* 49:2847–2851

28. Karimi S, Wong RJ, Holodny AI (2006) Skull Base, Orbital, and Perineural Involvement in Waldenström's Macroglobulinemia. *J Otolaryngol* 35:68. <https://doi.org/10.2310/7070.2005.4112>
29. Varettoni M, Defrancesco I, Diamanti L, et al (2017) Bing-Neel Syndrome: Illustrative Cases and Comprehensive Review of the Literature. *Mediterr J Hematol Infect Dis* 9:e2017061. <https://doi.org/10.4084/MJHID.2017.061>
30. Stacy RC, Jakobiec FA, Hochberg FH, et al (2010) Orbital involvement in Bing-Neel syndrome. *J Neuro-Ophthalmol Off J North Am Neuro-Ophthalmol Soc* 30:255–259. <https://doi.org/10.1097/WNO.0b013e3181dee96c>
31. Ettl AR, Birbamer GG, Philipp W (1992) Orbital Involvement in Waldenström's Macroglobulinemia: Ultrasound, Computed Tomography and Magnetic Resonance Findings. *Ophthalmologica* 205:40–45. <https://doi.org/10.1159/000310309>
32. Giarelli L, Melato M, Falconieri G (1982) Eye involvement in Waldenström's macroglobulinaemia. *Ophthalmol J Int Ophthalmol Int J Ophthalmol Z Augenheilkd* 185:214–219. <https://doi.org/10.1159/000309245>
33. Moulis H, Mamus SW (1989) Isolated trochlear nerve palsy in a patient with Waldenström's macroglobulinemia: complete recovery with combination therapy. *Neurology* 39:1399. <https://doi.org/10.1212/wnl.39.10.1399>
34. Lossos A, Averbuch-Heller L, Reches A, Abramsky O (1990) Complete unilateral ophthalmoplegia as the presenting manifestation of Waldenström's macroglobulinemia. *Neurology* 40:1801–1802. <https://doi.org/10.1212/wnl.40.11.1801-a>
35. Hellman JB, Harocopos GJ, Lin LK (2018) Waldenstrom macroglobulinemia involving the superior rectus muscle. *Am J Ophthalmol Case Rep* 10:304–306. <https://doi.org/10.1016/j.ajoc.2018.04.008>