American Journal of Ophthalmology Case Reports 20 (2020) 100926

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Case report

Corneal opacity and copper levels of the Lewis syndrome after systemic chemotherapy

Walter Lisch *, Urs Vossmerbaeumer

Department of Ophthalmology, University Medical Center of the Johannes Gutenberg- University Mainz, Mainz, Germany

ARTICLE INFO

Keywords:
Lewis syndrome
Discoid brownish opacification of Descemet membrane
Hypercupremia
Chemotherapy-induced normal level of copper in serum
Affinity of IgG to copper in Lewis syndrome
Unchanged corneal opacity after chemotherapy

ABSTRACT

Purpose: To report a female patient of biclonal Lewis syndrome which consists of a trias: biclonal gammopathy of undetermined significance, paraproteinemic keratopathy in form of a brownish discoid opacification at the level of Descemet's membrane and hypercupremia. After several years there was a conversion to multiple myeloma. Systemic chemotherapy led to a complete remission of multiple myeloma and to a normalization of the copper level in the blood that lasted five years. The corneal opacification remained unchanged.

Observations: A currently 66-year-old woman suffered from biclonal Lewis syndrome. On both eyes there is a central discoid yellow-brownish discoloration in the Pre-Descemet's layer. The corneal findings were unchanged after a follow up of eight years. However, there was a conversion to multiple myeloma (MM) type IgG with progressive anemia and suspicious bone lesions. A multiple systemic myeloma-therapy was indicated. Chemotherapy with subsequent tandem autologous-stem cell therapy (auto-SCT) was performed. The blood examination after this therapy showed a complete remission of multiple myeloma, and it was also very surprising that the serum copper level was within normal range. This finding remained unchanged over a period of five years. The bilateral corneal opacification was identical to that before chemotherapy. To the best of our knowledge, this represents the first observation of a normalization of copper levels in Lewis syndrome after chemotherapy.

Conclusions and importance: The Lewis syndrome represents a very rare disorder. The first case reported in Europe (Lisch et al., 2016)[1] showed a conversion from biclonal gammopathy of undetermined significance to MM after a follow-up of 17 years. Subjectively, the patient was in excellent health. The typical corneal, discoid brownish opacification at the level of Descemet's membrane is a suspicious hint of a copper disturbance for the ophthalmologist. The copper level of our patient was extremely elevated. The corneal opacification however, remained unchanged throughout the repeated ophthalmological examinations. In 2015, the conversion of our case with Lewis syndrome to MM performing chemotherapy in different steps and a twice auto-SCT resulted in a complete remission of MM and a normal range of the serum copper. The bilateral corneal opacification remained unchanged during an observation period of five years after chemotherapy.

1. Introduction

Monoclonal gammopathies (MG) are malignancies of plasma cells. Normal plasma cells help to defend the body against infection. Multiple Myeloma (MM) represents one part of the spectrum of monoclonal gammopathies that includes the much larger category of monoclonal gammopathy of undetermined significance (MGUS).[2] MGUS is one of the most frequent premalignant disorders in Western countries and occurs in approximately 3% of persons 50 years of age or older. MGUS is a hidden disorder because the patient has no subjective symptoms, and the hematologists see no reason to initiate therapy. It is proposed that regular check ups be performed annually. It is known that there is an association between MGUS and distinct corneal opacities in general, paraproteinemic keratopathy (PPK).[2] The MM- or MGUS-induced corneal crystals have been known for many years and are to be differentiated from cystinosis and Schnyder corneal dystrophy. Other bilateral opacifications have often been confused with different corneal dystrophies. Therefore, the term MG of ocular significance was also suggested.[3] Most of the MGUS-patients with an association of corneal opacity show serologically an IgG. One explanation could be that the IgG has a lower molecular weight than the other immunoglubulins and therefore can better penetrate into the cornea.[1] The Lewis syndrome

* Corresponding author. 155131, Mainz, Germany.
E-mail address: prof.dr.lisch@augenklinik-hanau.de (W. Lisch).

https://doi.org/10.1016/j.ajoc.2020.100926
Received 29 April 2020; Received in revised form 10 September 2020; Accepted 10 September 2020
Available online 18 September 2020

shows either a mono-or biclonal gammopatthy.

1.1. Case report

The female patient with biclonal Lewis syndrome is now 66 years old. In 2015 conversion to MM type IgG, type lambda with progressive anemia and suspicious bone lesions was diagnosed. MM-directed therapy was indicated. There were bilateral, discoid yellow-brownish corneal opacities at the level of Descemet's membrane (Fig. 1a and b). In vivo confocal laser scanning microscopy (IVCM) of posterior stroma revealed blurred structure of the keratocytes and hyperreflective punctiform and needle-like structures that seem to be typical for paraproteinemic keratopathy (Fig. 2). The conjunctiva, retina, and intraocular pressure were normal. There were no signs of intraocular inflammation. In the meantime, an age-related cataract proceeded and best corrected visual acuity (BCVA) decreased. Uneventful bilateral cataract surgery was performed. The BCVA after cataract surgery was 20/20 bilaterally despite the corneal opacities. The histopathological examination of the anterior lens capsule of both eyes and phacoemulsified lens material of the left eye did not show any copper deposits. High performance liquid chromatography of aqueous humor did not reveal any copper.The following current serological findings were collected: IgG, type lambda 66.2 g/l (norm 7–16 g/l); IgA, type lambda and IgM below reference; M-protein 45.5 lambda g/l; free light chain lambda 51.1 mg/l (norm 5.7–26.3 mg/l); free light chain kappa 8.6 mg/l (norm 3.3–19.4 mg/l); free kappa/lambda ratio 0.2 (norm 0.3–1.6); lambda light chain in 24-h urine 34.6 mg/l; hemoglobulin 9.5 g/dl (norm 12–15 g/dl). The serum copper levels showed a markedly elevated cooper level of 1326 μg/dl (norm 76–152 μg/dl). Serum coeruloplasmin within 0.23 g/l (norm 0.2–0.6 g/l), urine copper levels within 12 μg/dl (norm 10–60 μg/dl) and transaminases were within normal limits. After peripheral blood stem cell mobilization with cyclophosphamide, adriamycin, dexamethasone (CAD) and stem cell collection, tandem high dose melphalan therapy with auto-SCT was performed, followed byconsolidation therapy with bortezomib, lenalidomide, and deltasone. A complete remission of MM was achieved. Maintenance therapy with lenalidomide was stopped because of adverse effects. The last bone marrow biopsy in 2017 revealed 3% of plasma cell infiltration. A follow-up blood examination in 2020 showed a complete remission of MM. Serum copper level was within normal range of 144 μg/dl (norm 68–169μg/dl). A change in density of the brownish corneal opacities could not be determined after chemotherapy.

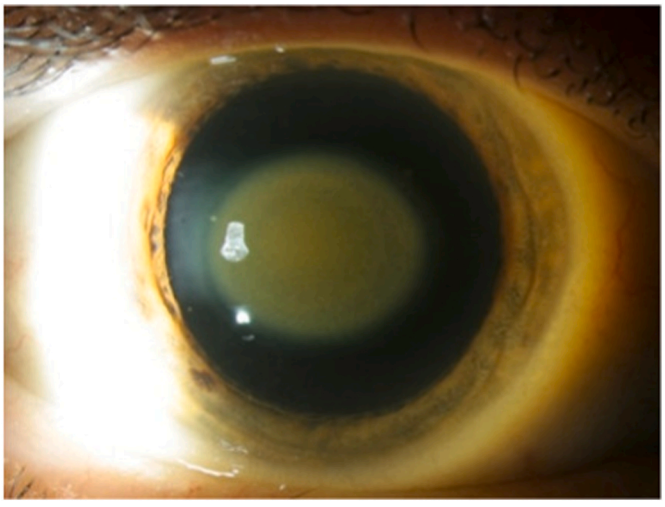

Fig. 1a. Central discoid, golden-brown discoloration of the proband's right cornea. Lisch et al. Trans Am Ophthalmol Soc 2016; 114: T7(1–21)

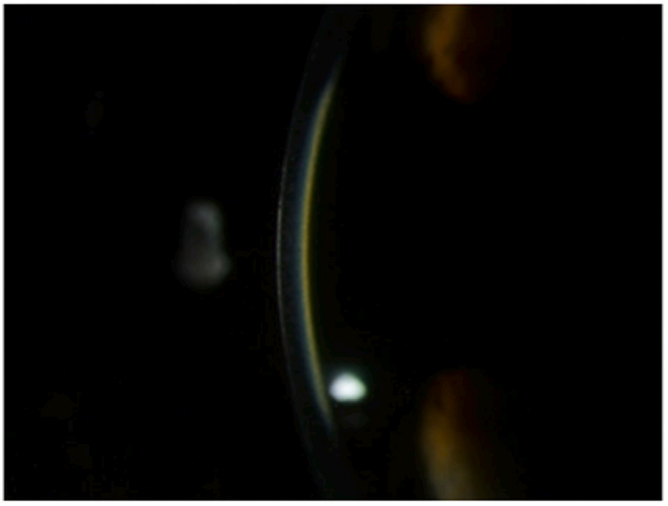

Fig. 1b. Slim slit corneal beam of Fig. 1a shows the location of the opacification at the level of posterior cornea. Lisch et al. Trans Am Ophthalmol Soc 2016; 114: T7(1–21).. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2. Discussion

Most MGUS patients show no subjective symptoms and clinical signs.[2] Hematologists do not see, in general, a need for therapy regarding MGUS.[4] Hematological check-ups are proposed once a year. MGUS is a hidden disorder. However, MGUS is one of the most premalignant disorders in the human body. A protracted premalignant stage (MGUS) precedes all cases of MM.[2] The posterior brownish sign of the cornea is suspicious for copper involvement.[5,6] The Lewis syndrome consists of either biclonal gammopathy of undetermined significance or of MGUS + hypercupremia + brownish opacification at the Descemet's layer of the cornea. There are only nine reported cases of monoclonal gammopathy with this special combination.[1] D-pencillamine or zinc gluconate are used with moderate success to lower the copper in the serum.[5-8] In only two publications of monoclonal gammopathies with hypercupremia and brownish discoloration of the posterior part of the cornea has the therapy of MM been reported in the literature.[5,6] Treatment of a 69-year-old woman with IgG MM + finely granular discoloration of the corneal endothelium + high copper levels in the blood consisted of blood transfusions, irridation to the vertebral column, and an initial brief course of cyclophosphamide.[5] The IgG showed 3240 mg per 100 ml (normal values are given at 620 t 1400), and depression of IgA and IgM. D-pencillamine was then administered in oral dose each day.However, no significant decrease in serum copper was observed. A 41-year-old female patient showed a Lewis syndrome of a monoclonal IgG with a bilateral central, golden-brown discoloration of the deep layers of the cornea and a similar staining beneath the anterior and posterior capsules of each lens.6 A 10-week course of penicillamine chelation treatment resulted in 44% reduction in serum copper. A trial with 2 courses of melphalan (8mg) daily initiated with prednisone (120 mg) daily for 4 days resulted in only a moderate decrease in IgG levels. Lewis et al.[7] and Baker and Hultquist[9] presented an intensive chemical and biological investigation of copper with regard to this female patient. The authors reported a 30-year long term follow-up of this patient [10] who was first examined in 1975.[6] She was in excellent health. The only apparent systemic manifestation of hypercupremia was her copper-colored hair. In addition to her unchanged corneal opacities, the anterior and posterior lens capsules were coated with copper-colored material. The authors interpreted their case as unique because of this long-term follow up and the patient's benign clinical course of multiple myeloma. In our patient the lens didn't show any copper deposits and her hair was not copper-colored. The major difference is our patient had

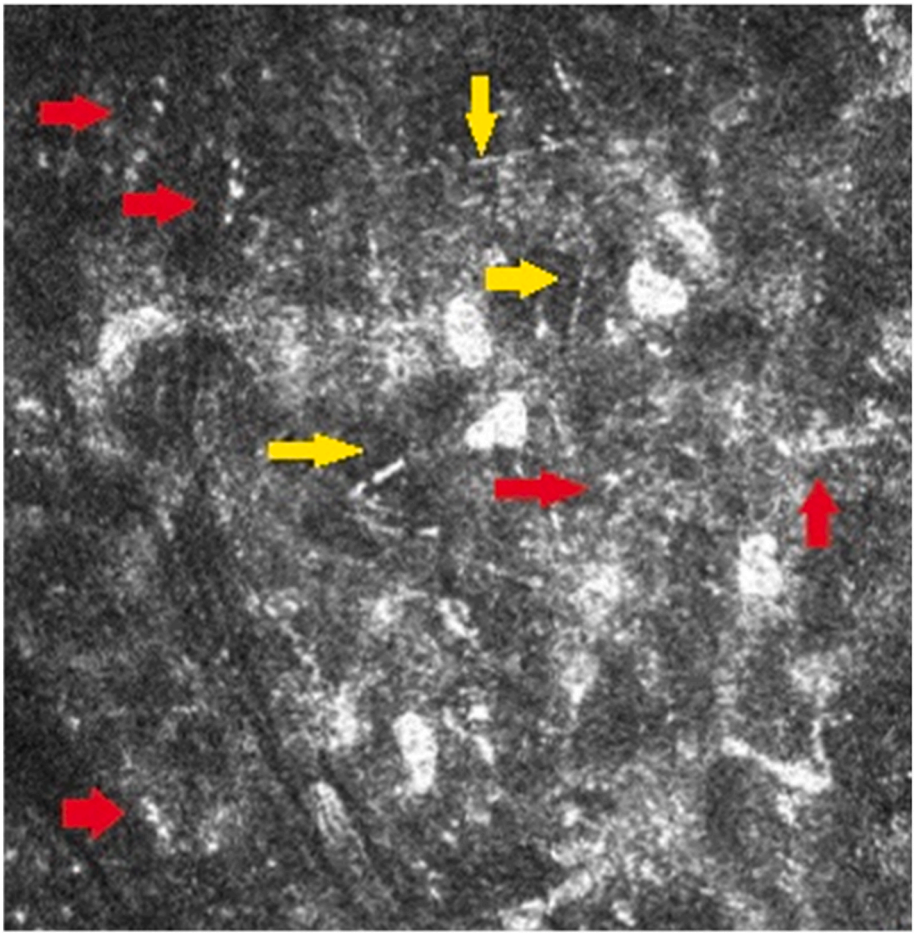

Fig. 2. Proband's confocal laser scanning microscopy of posterior stroma (341μm) reveals hyperreflective punctual (red arrows) and needle-like structures (yellow arrows), typical for PPK.. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

normal copper levels in the serum after the current and modern chemotherapy of MM during a follow-up of five years. To date, however, no improvement in the existing corneal changes has been observed despite normal copper levels in the blood. Subjectively, our patient was in excellent health before and after the MM treatment. Normally, copper does not bind to immunoglobulins.[5] In the case of Lewis syndrome the IgG has a marked affinity for copper.[6,9] The chemotherapy of our proband led to a complete remission of the MM and at the same time to normal copper values in the serum over five years. This is further evidence of the unique IgG nature in the context of Lewis syndrome. The Lewis IgG must have a special, unknown property with regard to copper binding. Further studies are needed to clarify this mechanism.

Patient consent

This report does not contain any personal identifying information.

Funding

No funding or grant support

Authorship

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

Funding

Funding was received for this work.
No funding was received for this work.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Authorship

The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All listed authors meet the ICMJE criteria.
We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

One or more listed authors do(es) not meet the ICMJE criteria.

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

Contact with the editorial office

This author submitted this manuscript using his/her account in EVISE.

We understand that this Corresponding Author is the sole contact for the Editorial process (including EVISE and direct communications with the office).He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

We confirm that the email address shown below is accessible by the Corresponding Author, is the address to which Corresponding Author's EVISE account is linked, and has been configured to accept email from the editorial office of American Journal of Ophthalmology Case Reports:

Someone other than the Corresponding Author declared above submitted this manuscript from his/her account in EVISE:

We understand that this author is the sole contact for the Editorial process(including EVISE and direct communications with the office). He/she is responsible for communicating with the other authors, including the Corresponding Author, about progress, submissions of revisions and final approval of proofs.

Declaration of competing interest

The following authors have no financial disclosures: W.L.,U.V.,M.M.

Acknowledgements

None.

References

1. Lisch W, Wasielica-Poslednik J, Kivelä T, et al. The hematological definition of monoclonal gammopathy of undetermined in relation to paraproteinemic keratopathy (an American Ophthalmological Society Thesis). *Trans Am Ophthalmol Soc*. 2016;114(T7):1–21.
2. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006;354:1362–1369.
3. Karakus S, Gottsch JD, Caturegli P, Eghrari AO. Monoclonal gammopathy of "ocular" significance. *Am J Ophthalmol case reports*. 2019;15:100471, 1-5.
4. Rajkumar SV, Dimopoulos MA, Palmubo A, et al. International myeloma working group updated criteria fort the diagnosis of multiple myeloma. *Lancet Oncol*. 2014; 15:e538–e548.
5. Goodman SI, Rodgerson DO, Hypercupremia J Kauffman. In a patient with multiple myeloma. *J Lab Clin Med*. 1967;70:57–62.
6. Lewis RA, Falls HF, Troyer DO. Ocular manifestations of hypercupremia associated with multiple myeloma. *Arch Ophthalmol*. 1975;93:1050–1105.
7. Lewis RA, Hultquist DE, Baker BL, et al. Hypercupremia associated with a monoclonal immunoglobulin. *J Lab Clin Med*. 1976;88:375–387.
8. Probst LE, Hoffman E, Cherian MG, et al. Ocular copper deposition associated with benign monoclonal gammopathy and hypercupremia. *Cornea*. 1996;15:94–96.
9. Baker BL, Hultquist DE. A copper binding immunoglobin from a myeloma patient. Purification, identification, and physical characterization. *J Biol Chem*. 1978;253: 1195–1200.
10. Garg S, Jampol LM, Lewis RA, Penner JA. Corneal copper deposition secondary to a variant of multiple myeloma: 30-year catamnesis. *Arch Ophthalmol*. 2006;124: 130–132.