CASE REPORT

Fatal lymphomatoid granulomatosis with primary CNS-involvement in an immunocompetent 80-year-old woman

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SUMMARY

An 80-year-old woman presented with weight loss, fatigue, dizziness and a brain stem lesion. Extensive work-up revealed lymphomatoid granulomatosis (LYG) with primary clinical manifestation in the central nervous system (CNS), a rare Epstein-Barr virus-driven multisystem lymphoproliferative disorder, to be causative for the symptoms. Immunochemotherapy consisting of rituximab and temozolomide was started, but the disease progressed and the patient subsequently died. Histology, diagnostic criteria, differential diagnosis and treatment options for LYG with CNS involvement are discussed. This case demonstrates that LYG with CNS involvement may necessitate more aggressive treatment approaches than combination therapy with rituximab and temozolomide.

BACKGROUND

Lymphomatoid granulomatosis (LYG) is a rare lymphoproliferative disease. It may affect multiple organs including the central nervous system (LYG-CNS). The lungs are usually affected at diagnosis of LYG, but involvement of the kidneys, the central and peripheral nervous system, and the skin, along with constitutional symptoms, are also reported.¹ While LYG is mainly seen in immunocompromised patients suffering from AIDS, cases of solid-organ transplantation and in others,^{2–3} there are reports on LYG in immunocompetent persons as well.^{4–5} Presentation of LYG with initial CNS symptoms is rare. In 2009, Lucantoni *et al*⁶ reported on four patients with isolated LYG-CNS and identified another 18 cases in the literature with one more patient reported recently.⁷ Moreover, only about one-third of all patients with LYG develop CNS symptoms during the course of the disease.⁸

Thus, treatment of LYG with CNS involvement resides on anecdotal reports. Since there are no randomised treatment trials on LYG with CNS involvement, knowledge on this rare condition relies on the report of single cases.

CASE PRESENTATION

An 80-year-old woman was admitted to an outside hospital with nausea, vomiting and dizziness. The patient reported weight loss of 12 kg (19% of her body weight) and fatigue during the past 6 months. Further medical history was remarkable for surgically treated adenocarcinoma of the rectum 5 years earlier (pT2 N0 R0 G2), hypothyroidism and migraine with aura. The patient was otherwise

healthy and had not undergone chemotherapy, radiation or immunosuppressive treatment at any time. Family history was unremarkable. On initial presentation, the patient was afebrile, and general medical and neurological examinations were unremarkable, except for high blood pressure levels (210/90 mm Hg, 60 bpm). Standard laboratory values were unremarkable. Chest radiography and sonography of the abdomen and thyroid were unremarkable as well. The patient's dizziness improved slightly after controlling of her blood pressure. In the following week the patient's status deteriorated. She developed diplopia, right-sided peripheral facial and abducens nerve palsy and increasing dizziness. No other signs were noticed.

INVESTIGATIONS

The patient underwent cranial MRI and lumbar puncture. MRI revealed a linear contrast-enhancing lesion in the mesencephalon, reaching the fourth ventricle, suggesting an inflammatory or neoplastic aetiology (figure 1A, E). Empirical antiviral and antibacterial therapy with ceftriaxone and aciclovir was started. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis. Serological testing for herpes simplex, varicella virus and borrelia was negative, as was microbial testing for listeria and meningococci, the bacterial cultures being sterile. Later, another MRI showed a progressive lesion with nodular enhancement (figure 1B, F). MR-spectrometry resulted in a marked decrease of N-acetyl-aspartic acid with peaks at 1.33 ppm for lactate and lipid, respectively. Anti-infective therapy was stopped and the patient was referred to our hospital.

Extensive diagnostic workup was performed. Electrophoresis showed increased α 1-globuline and α 2-globuline fractions, suggestive of acute inflammation. Testing for paraprotein remained negative. Repeated CSF analysis again showed T-cell dominated lymphocytosis (53/ μ L) with increased protein (1036 mg/L) and lactate (3.31 mmol/L), as well as identical oligoclonal bands in serum and CSF. Cytological examination of CSF demonstrated no evidence for blasts, tumour cells or granulocytosis. Routine peripheral blood analysis, including complete blood count, was normal. Analyses for tick-borne encephalitis, herpes simplex, measles, rubella and varicella zoster virus were negative. Analysis for Epstein-Barr virus (EBV) showed increased titres of EBV-anti-viral capsid antigen (VCA) IgA antibody (1:640) and EBV-anti-early antigen (EA) antibody, suggestive of EBV-reactivation. PCR-amplification

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Figure 1 (A–G) Progression of the cerebral lesion and histology of the pulmonary lesion. (A and E) initial MRI; (B and F) MRI after a course of ceftriaxone and aciclovir 12 days later; (C and G) MRI after another 23 days; (D and H) MRI 47 days after the initial MRI. A–D are fluid attenuation inversion recovery, E–H are T1 postcontrast. I–M Histology of the pulmonary lesion. (I) H&E stain demonstrating angiocentric growth; (K) immunostaining for CD20; (L) immunostaining for Molecular Immunology Borstel-1 (Ki-67); (M) In-situ hybridisation for EBV (EBV-encoded small RNA). Bar=50 μ m.

of EBV in the serum showed 2800 copies/mL, reflecting low copy numbers. Results for hepatitis B, hepatitis C and HIV were negative, as were the results of testing for borrelia and syphilis. Analysis of adenosine-deaminase excluded adenosine-deaminase deficiency. Determinations of lysozyme, ACE and interleukin-2 receptor resulted in normal values. CT of the chest and abdomen revealed multiple bilateral pulmonary lesions (figure 2).

Mammography and breast sonography showed no relevant pathology. Since the brain stem lesion was inaccessible for biopsy, CT-based biopsy of a pulmonary lesion was performed. Two days after biopsy, the patient deteriorated further, becoming comatose, necessitating intubation and mechanical ventilation. Immediate cranial CT was performed after intubation, revealing an acute occlusive hydrocephalus due to progression of the brainstem

Figure 2 Pulmonary involvement of lymphomatoid granulomatosis. Chest CT shows several pulmonary nodules (arrows) throughout both lungs (A–D). All lesions are less than 1 cm in diameter and are preferentially located along the bronchovascular structures or interlobular septa. Eventually, CT-guided biopsy of the largest pulmonary nodule (D) was performed for histological diagnosis.

lesion occluding the fourth ventricle. Therefore, extraventricular drainage was placed.

Histological examination revealed polymorphic lymphoid infiltrates with focal necrosis (figure 1I). Atypical large B lymphocytes were demonstrated, staining strongly positive for CD20 with high MIB1-index (Ki-67), as seen in figure 1K, L. In-situ hybridisation of these cells (figure 1M) was highly positive for nuclear EBV (EBER). Moreover, there was focal angiocentric growth of proliferating atypical cells with abundant T lymphocytes. Staining for KL1, CK7, ALK1, CD30, S100 and CD1a was negative. Another repeated CSF analysis demonstrated sparse blasts, staining positive for CD20. Histology of the pulmonary lesion is most consistent with high-grade LYG.

DIFFERENTIAL DIAGNOSIS

The presentation of peripheral palsies of two cranial nerves together with nausea, vomiting and dizziness points to a lesion of the brain stem. Weight loss and fatigue are compatible with chronic infection or inflammation, including sarcoidosis, coccidioidomycosis, tuberculosis and different kinds of lymphoma,¹ and—especially in light of the patient's previous malignant disease—with metastasis, which were all ruled out by imaging, CSF and serological studies as well as histology. Similar radiographic and CSF findings have been associated with CLIPPERS syndrome (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids,⁹ although a recent report suggested some overlap with LYG.¹⁰

TREATMENT

The patient was started on high-dose dexamethasone (8 mg four times daily), and immunochemotherapy consisting of rituximab (375 mg/m²) and temozolomide (150 mg/m² for 5 days) was initiated.

OUTCOME AND FOLLOW-UP

After initiation of immunochemotherapy, CD20-positive cells were no longer detectable. Despite treatment, the tumour progressed (figure 1C, G before and D, H after immunochemotherapy) and the patient died in the hospital 2 months after initial presentation and 8 months after her symptoms first appeared.

DISCUSSION

The patient's clinical course and histology—without evidence of recurrence of the adenocarcinoma of the rectum—were consistent with LYG, an EBV-associated lymphoproliferative disorder, considered a T-cell rich form, among the diffuse large B-cell lymphomas,¹¹ first described by Liebow *et al*¹² (for overview see Roschewski and Wilson¹). In general, diagnosis and grading is based on pulmonary biopsy,¹ as was the case in our patient.

Since this patient's brain stem lesion was inaccessible for biopsy, diagnosis was based on radiological evidence and lung histology. LYG has been demonstrated to affect several brain regions. Involvement of the white matter, deep gray matter and the brain stem seem to be the most often affected sites.¹³ Furthermore, there are several radiological patterns of LYG with CNS-involvement as reviewed by Tateishi *et al*.¹⁴ Multiple punctate or linear enhancements along the perivascular space have been implicated in LYG, but cases with nodular or ring-like enhancement and even large masses and leptomeningeal enhancement have been reported.¹⁴ Initial MRI demonstrated linear enhancement. Follow-up MRI was consistent with nodular lesions. MR-spectrometry was non-specific and could not rule out glioma, while being, nonetheless, consistent with inflammatory changes. Lacking brain stem histology, we cannot

definitely rule out other diseases to the brain stem, but the typical images appearing on repeated MRI-scans and positive histology from the lung render LYG as the most likely.

Histologically, LYG is defined by angiocentric and angiodestructive growth in combination with necrosis and infiltration of vessel walls.¹ Diagnostic criteria were suggested by Katzenstein *et al*.⁸ Neurological presentation may include symptoms of the central and peripheral nervous system. While affection of the peripheral nervous system with paresthesias is considered uncommon, central nervous system involvement may affect about one-third of all patients with LYG over the course of the disease. Moreover, CNS involvement may be a poor prognostic indicator. A wide range of signs in CNS-LYG have been described, including cranial nerve palsies, ataxia, change in mental status, hemiparesis and seizures. Our patient presented with signs of CNS involvement, without symptoms of pulmonary or other organ involvement, initial chest radiography being unremarkable.

The pathogenesis of LYG remains elusive, but a defect in T-cell activity, allowing EBV-infected B cells to express EBV-encoded proteins, which results in disturbance of the interaction between B cells and T cells and consecutive lymphoproliferation, has been hypothesised.⁴ Thus, EBV plays a pivotal role in LYG pathogenesis, placing LYG in the group of EBV-related disorders along with Burkitt's and Hodgkin's lymphoma, nasopharyngeal carcinoma, some diffuse large-cell B-cell lymphomas and others.¹⁵ Consistent with these observations, EBV replication was detected in the serum of our patient by PCR.

LYG is a rare disease. Thus large prospective randomised controlled trials have not been undertaken and treatment is merely based on anecdotal reports. To date, multiple regimens have been implicated in the treatment of LYG, with some regimens derived from immunomodulatory approaches and others from cancer therapy. Suggested regimens include corticosteroids, rituximab and interferon α -2b. For high-grade LYG, immunochemotherapy consisting of rituximab, etoposide, prednisone, vincristine, adriamycin and cyclophosphamide has been suggested.¹ In our patient, such an aggressive approach did not appear feasible as there was a need for invasive critical care, including mechanical ventilation and external CSF drainage. There have been reports suggesting rituximab alone^{3 16–18} or in combination with temozolomide as a successful treatment option for LYG and also for lymphomas of the central nervous system.^{19–21} Nonetheless, failure of treatment with rituximab monotherapy has been reported.²² The lacking efficacy of rituximab, temozolomide and dexamethasone in this patient underscores the need for more aggressive, but well-tolerated, approaches for high-grade LYG of the central nervous system.

Learning points

- ▶ Although lymphomatoid granulomatosis (LYG) with central nervous system (CNS) involvement is a rare condition, its diagnosis should be borne in mind, especially in patients with brain stem lesions and signs of multisystem disease.
- ▶ Previous case reports have been in favour of rituximab with or without temozolomide for LYG with CNS involvement.
- ▶ Treatment failure in this case illustrates that in patients with high-grade LYG of the CNS, more aggressive treatment approaches are warranted—even (or especially) if invasive measures such as mechanical ventilation or external ventricular drainage are needed.

Contributors DO, M Hagge, H B Huttner, S Schwab and RL treated the patient during her stay in our hospital, reviewed the literature on lymphomatoid granulomatosis and all authors provided important intellectual content on the case. AA performed the histology on lung biopsy samples and contributed to the figures. SK performed and evaluated the MRI-scans of the patient and contributed to the figures.

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