CASE REPORT

More than a headache: a case of cetuximab-induced aseptic meningitis

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SUMMARY

While the wide belief is that monoclonal antibodies, due to their large size, would not be able to penetrate the blood–brain barrier, we present a rare case of aseptic meningitis induced by intravenous cetuximab administration. A 58-year-old man with tonsillar squamous cell cancer presented with headache and fever, which started approximately 1 h after his first dose of cetuximab (loading dose of 400 mg/m^2 equalling 800 mg). CT scan of the head was non-revealing and laboratory tests including complete blood count, serum comprehensive metabolic panel and coagulation profile were within normal limits. Aseptic meningitis in the setting of cetuximab therapy has been reported on 6 previous occasions. Consistent with these prior reports, it is interesting to note that this case also occurred after administration of the initial higher loading dose of Cetuximab. This is of interest as Cetuximab is more frequently being dosed at 500 mg/m^2 (higher dose) every 2 weeks in colorectal cancer.

BACKGROUND

Cetuximab is a recombinant human/mouse chimeric monoclonal antibody which binds specifically, and competitively inhibits the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1). It has been approved for use in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN), and for metastatic colorectal cancer (CRC) in patients with EGFR-expressing tumours.[1] In this report, we present a case of aseptic meningitis induced by intravenous cetuximab administration.

CASE PRESENTATION

A 58-year-old man with recent diagnosis of right tonsillar Squamous Cell Cancer was emergently admitted to the hospital for symptoms of headache and fever, which started approximately 1 h after his first dose of cetuximab (loading dose of 400 mg/m^2 equalling 800 mg). He also received diphenhydramine as a premedication. His medical history included infection with HIV on antiretroviral therapy (lamivudine/norvir/retrovir), hypertension (on amlodipine, clonidine and aspirin), hyperlipidaemia (on lipitor) and chronic kidney disease (CKD) stage V (on bicitra and calcitriol), not yet requiring dialysis. The patient was seen in the emergency room 4 h after chemotherapy, where he was febrile to 102°F, with chills and a persistent headache. The headache was described as frontal and 10/10 in severity, with no radiation. There was no neck-stiffness, photophobia, nausea or vomiting, but given his HIV status, there was a high suspicion for infectious meningitis.

INVESTIGATIONS

CT scan of the head was non-revealing and cerebrospinal fluid (CSF) studies were promptly sent, showing a neutrophil predominant pleocytosis to 473 white cell counts (WCCs)/mm^3 (80% neutrophils) in CSF tube 1 and 500 WCCs/mm^3 (62% neutrophils) in CSF tube 4. Red blood cells were 150 and 50 cells/mm^3, respectively. CSF protein was elevated to 128 mg/dL and glucose was normal at 66 mg/dL. Other laboratory tests including complete blood count, serum comprehensive metabolic panel and coagulation profile were within normal limits.

DIFFERENTIAL DIAGNOSIS

Infectious aetiologies were highest on the differential, with viral being more likely than bacterial. Extensive CSF studies were performed including bacterial antigens for *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Cryptococcus*, and a viral encephalitis panel that included herpes simplex virus types 1 and 2, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, Varicella-Zoster virus, West Nile virus, Saint Louis encephalitis virus, and adenovirus and enterovirus. While cerebral toxoplasmosis was on the differential, the patient was not immunosuppressed, with a CD4 count of 486 cells/mm^3, viral load less than 19 copies/mL and a negative CT scan. Serologies were not helpful at this point, since the patient had prior serologies positive for *Toxoplasma* from as far back as 2004.

His medication regimen indicated above was ruled out for medication interaction. The temporal relation of the symptoms beginning several hours after his first treatment with cetuximab was hard to ignore.

TREATMENT

The patient was empirically treated with dexamethasone, vancomycin, ceftriaxone and ampicillin, while awaiting CSF cultures. CSF bacterial antigens were negative, after which the dexamethasone was discontinued. The patient was provided supportive care with intravenous fluids and acetaminophen. Antibiotics were discontinued on day 4 of presentation once the CSF cultures were confirmed as negative. The CSF viral encephalitis panel returned negative as well. The patient reported symptomatic improvement by day 2 and was discharged home with no additional medications on day 4.

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OUTCOME AND FOLLOW-UP

Alternative chemotherapy regimes for treatment of SCCHN include 5-fluouroracil, taxanes and platinum. However, these were not a feasible option for our patient given his CKD stage V (predialysis). The other, less preferable option was to provide radiotherapy alone without chemotherapy. The patient was counselled on the risk of recurrence versus benefits of rechallenge with a lower dose of the drug. On day 7, the patient received his second dose of cetuximab at 250 mg/m^2 as planned for his chemotherapy regimen, with no adverse reaction.

This patient has continued following up with our clinic even after this presentation and, unfortunately, due to radiation-induced mucositis, his health deteriorated, requiring him to subsequently be on haemodialysis, with lower CD4 counts than prior. Despite this, the patient continued with five rounds of cetuximab and never had recurrence of the earlier symptoms or others suggestive of intracranial infection. This makes us fairly certain that the episode in question was in relation to his initial cetuximab dosing.

DISCUSSION

A clinical presentation of meningitis raises suspicion for bacterial infections, which require aggressive therapy. Aseptic meningitis refers to a similar clinical picture, with concurrent CSF pleocytosis indicating meningeal inflammation, but in the absence of positive cultures. In contrast to bacterial meningitis, most cases of aseptic meningitis are self-limited and resolve with supportive care. Aseptic meningitis in the setting of cetuximab therapy has been reported on six previous occasions.[2–5] It is interesting to note that all these reports involved patients with head and neck malignancies.

Historically, aseptic meningitis has been described with intravenous immunoglobulin infusions.[6 7] The hypothesis is that IgG can cross the blood–brain barrier (BBB) and is the inciting factor for the inflammatory cascade.[8] While the wide belief is that monoclonal antibodies, such as trastuzumab and cetuximab, would not be able to penetrate the BBB due to their larger biochemical size, there have been reports of trastuzumab levels measured in the CSF after intravenous administration.[9] While an ELISA technique has been described[10] to measure these levels, this test is not commercially available, making it difficult to definitively prove the aetiology.

In our case, the chronology of events, and clinical and laboratory findings, all favour the diagnosis of aseptic meningitis. While there are no tests to reliably support causality, the temporal sequence of drug infusion and symptom onset raises the possibility of cetuximab leakage or penetration into the CSF and subsequent aseptic meningitis. It is interesting to note that this case was also due to an initial high dose of cetuximab, as reported previously. This is of interest, as cetuximab is more frequently being dosed at 500 mg/m^2 (higher dose) every 2 weeks in CRC.

Monoclonal antibodies have a significant role in treatment of diseases outside oncology, such as multiple sclerosis (MS). Extensive research in MS has been performed on the ability of monoclonal antibodies to cross the BBB while tagged to T cells.[11] In MS, however, pre-existing inflammation was identified to be a cause for the T cell leak into the CSF. Also, there have been studies implicating inability of cetuximab to cross the BBB when intact.[12] Although it is unclear at this time what the exact mechanism behind a proposed cetuximab CSF leak is, it is possible that the release of proinflammatory cytokines with use of EGFR inhibitors[13] may disrupt the BBB and enable entry into the CSF. However, why the higher dose and not the lower dose would cause this, is still unclear. Only one case in the past has been noted to have a recurrence with lower dosing of the cetuximab.[2] Further molecular research is needed to better understand the mechanism of the leak of cetuximab into the CSF and the resultant inflammatory cascade.

Learning points

- Aseptic meningitis should be watched for in patients receiving loading doses of monoclonal antibodies.
- Until a test to identify a suspected agent in CSF becomes commercially available, drug induced aseptic meningitis will still be a diagnosis of exclusion, with history and chronology playing key roles.
- All case reports thus far, with exception of one case, have been promising with respect to rechallenge with lower doses of cetuximab, that is, it has not been associated with recurrence of symptoms.
- Further molecular research will improve our understanding of the mechanism behind this inflammatory cascade.

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