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Case Report Open Access

Cetuximab Induced Aseptic Meningitis: A Rare Side Effect

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Abstract

A 65-year-old African American female was diagnosed with laryngeal cancer ($T_1N_2M_0$) in August 2015. She received platinum-based chemotherapy initially. After an initial remission patient had a systemic recurrence which was treated with Cetuximab. The patient presented to ER six hours after receiving the first dose of cetuximab with high grade fever and signs of meningeal irritation. CSF analysis showed neutrophil predominant pleocytosis with negative gram stain and culture. It was concluded that the patient had cetuximab induced aseptic meningitis. The patient was re-challenged with lower dose of cetuximab which was tolerated well. Cetuximab induced aseptic meningitis is a rare side effect reported in handful of cases.

Keywords: Cetuximab; Aseptic meningitis; Laryngeal cancer; Meningeal irritation; Chemotherapy

Introduction

Cetuximab is a chimeric IgG1 monoclonal antibody against EGFR and is used for EGFR expressing metastatic colorectal cancer and squamous cell cancer of head and neck [1]. The common side effects of cetuximab include infusion like reaction, cytokine release syndrome, rash, dry skin and nail changes, nausea, malaise, fatigue and transaminitis [2]. Aseptic meningitis is a rare side effect and there are only few case reports describing this effect. We report a case of aseptic meningitis after the first dose cetuximab in a patient with metastatic head and neck cancer.

Case Presentation

Our patient is a 65-year-old African American female with past medical history of COPD, Hepatitis C s/p treatment, ex-smoker with 45 pack years who was diagnosed with laryngeal cancer ($T_1N_2M_0$) in August 2015. She initially received induction chemotherapy with docetaxel, 5-flurouracil and cisplatin for three cycles followed by concurrent chemo-radiation therapy with carboplatin with complete response. Sixteen months later, she had her first recurrence as a solitary lung nodule which was treated with wedge resection of lung and adjuvant radiotherapy, following which she had second recurrence six months later in pre-carinal and mediastinal nodes. In view of poor tolerance of previous chemotherapy, decision was made to start her on single agent Cetuximab.

Earlier on the day of admission, patient had received her first dose of cetuximab (700 mg as 400 mg/m^2) after pre medication with H1 antagonist, diphenhydramine 25 mg IV. She returned to ER 6 hours after treatment at cancer center with a fever of 103 F and chills. She exhibited photophobia, neck stiffness and headache. Vital signs on admission were: Temperature 39.1°C, BP 170/91 mmHg, HR 89/min, RR 14/min with oxygen saturation of 97% on room air. Her physical exam was unremarkable except for neck rigidity. Rest of the neurological exam was benign.

Laboratory data on admission showed WBC 3.00 per microliter, Hb 11.5 g/dL, Hct 32.3, Platelets 100 per microliter, absolute neutrophil count of 2800, C-reactive protein was normal at 1 mg/dL. CT scan of the head without contrast was performed which showed no acute intracranial findings. The patient was started on empiric broad spectrum antibiotics after lumbar puncture was performed. CSF analysis showed normal glucose (48 mg/dL), elevated protein (111.7 mg/dL), WBC of 321/ul with neutophilic pleocytosis. PMN were 91% and 3% were lymphocytes.

CSF Gram stain, culture, PCR for viruses and cryptococcal antigen were negative. Blood cultures remained negative. Antibiotics were stopped on day 3 of admission after all workup came back negative and patient was afebrile. At the same time clinically the patient improved with resolution of headache and photophobia. It was concluded that the patient had aseptic meningitis likely due to cetuximab. After two weeks, patient successfully received re-challenge at a dose of 250 mg/m^2; 435 mg with 12 mg of dexamethasone and 25 mg of diphenhydramine as premedication. Until this report she has completed 3 more weekly doses without any recurrence of meningeal irritation.

Discussion

Aseptic meningitis refers to clinical and laboratory evidence of meningeal inflammation with negative bacterial culture. Enteroviruses are the most common causes. Other causes include fungi, medications for example, infliximab, azathioprine, NSAIDs. It has also been associated with malignancies and autoimmune disease like sarcoidosis and SLE [3]. Aseptic meningitis has been reported as a rare side effect of cetuximab therapy. The first occurrence of drug-induced aseptic meningitis related to cetuximab was reported in 2000 by Baselga et al. in a phase I clinical trial [4]. Most of the literature is limited to case reports which describes this side effect within the first 24 hours after the first dose (Table 1) [1]. The diagnosis is largely one of exclusion after ruling out bacterial and viral etiologies. It is treated with empiric antibiotics until a microbiologic diagnosis is established as in our case.

The mechanism is largely unknown. Aseptic meningitis has been reported to be associated with other immunoglobulin treatment including IVIG [1,4,5]. It has been postulated that IgG can cross the blood brain barrier and induce inflammatory reaction in the meninges and cetuximab could potentially share the same mechanism [1,5]. Other possible mechanisms include hypersensitivity reaction which could

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Article	Age of patient	Diagnosis	Dose (mg/mt^2)	Symptoms	Time of onset	CSF findings	Treatment and time to recovery	Re-challenge/dose/ premedication
[1]	66 y	Locally advanced laryngeal SCC	400	Headache, neck stiff ness photophobia nausea vomiting	Few Hours	WBC 4100/ul. PMN pleocytosis (90%) High protein (1.5 g/L) Normal Glucose Negative bacterial and viral culture	Empiric antibiotic/ Recovery within several days.	Negative re-challenge after 28 days, 250 mg/mt^2 with SMD and DPH.
[6]	58 y	Tonsillar SCC	400	Frontal headache Fever	1 hour	WBC 473/ul PMN pleocytosis (80%) High protein (1.28 g/L Normal Glucose	Empiric antibiotic/ Recovery within 4 days	Negative re-challenge at dose 250 mg/mt^2
[7]	78 y	NSCLC	400	Severe headache, nausea, vomiting	Few Hours	WBC 528/ul. PMN pleocytosis (87%) High protein Normal glucose	Empiric antibiotic/ Recovery time not reported	Not reported
[7]	59 y	Metastatic NSCLC	400	Acute encephalopathy	Few	Elevated protein (1.16 g/L). Cell count and differential not reported. Negative culture	Empiric antibiotic/ Several days	Not reported
[8]	54 Y	Squamous cell maxillary cancer	400	Frontal headache, neck discomfort, Fever 39.9°C fever	Few Hours	WBC 1025/ul. PMN pleocytosis (92%) High protein (1.65 g/L) Normal glucose Negative culture and HSV PCR	Empiric antibiotic/ Recovery time not reported	recurrence of symptoms after rechallenge at 250 mg/mt^2. 3rd and subsequent re-challenges were unremarkable.
[9]	45 y	Recurrent SCC of larynx	400	Frontal headache, Fever 38.3°C	Few Hours	WBC 2300/ul. PMN pleocytosis (98%) High protein (1.04 g/L) Normal glucose Negative culture	Empiric antibiotic, acyclovir/Recovery time not reported	Successful at 1 week, 250 mg/mt^2/ DPH
[9]	42 y	Locally advanced SCC of Rt tonsil	400	Frontal headache, Fever 39.4°C Photophobia	8 Hours	WBC 2267/ul PMN pleocytosis (90%) High protein (1.46 g/L) Normal glucose Negative culture	Empiric antibiotic, acyclovir. DEX/ Recovery at 12 days.	Successful at 2 weeks/250 mg/mt^2/ DPH and DEX
[10]	67 y	Recurrent oropharyngeal SCC	400	Fever 39.2°C Headache	9 Hours	WBC 1413/ul PMN pleocytosis (92%) High protein (1.79 g/L) Normal Glucose Negative culture and serology.	Empiric antibiotic and DEX/Recovery within 14 days	Patient refused re-challenge.
Current case	65 y	Metastatic laryngeal cancer	400	Fever 39.4°C Headache Photophobia	6 hours	WBC 321/ul PMN pleocytosis (91%) High protein (1.1 g/L) Normal Glucose Negative culture HSV PCR negative	Empiric antibiotic/ Recovery within 5 days.	Negative re-challenge after 2 weeks/250 mg/ mt^2, DEX and DPH.

DEX: Dexamethasone, SMD: Solumedrol, DPH: Diphenhydramine. PMN: Polymorphonuclear Leukocytes. SCC: Squamous Cell Carcinoma. NSCLC: Non-Small Cell Lung Cancer

Table 1: Review of the case reports.

explain the response to steroid treatment and the use of higher initial loading dose. Chung et al postulated possible IgE mediated reaction related to cetuximab infusion [6-10]. The identified antigen was an oligosaccharide on the fab portion of cetuximab molecule. People who were previously sensitized with either food, tick bites or some parasites had IgE against cetuximab.

Recovery is expected within 1-2 weeks after withdrawal of drug [11]. In our patient, it took three days to recover. Re-challenge with cetuximab even at a reduced dose has been reported to have resulted in recurrence [9] though of the 8 previously reported cases, 2 studies did not report rechallenge, one patient refused rechallenge and in 4 out of five cases rechallenge was successful. Premedication with steroids and restarting at lower dose are reported to be useful which has been seen in our patient [1,10]. Though in our patient, we were able to give cetuximab at recommended maintenance dose of 250 mg/m^2.

Cetuximab is used for both colorectal and head & neck SCC. Interestingly, majority of the published case reports of aseptic meningitis were with head and neck cancers. The first 2 cases reported

were, however, in NSCLC [8]. Grandvuillemin et al studied 602 adverse drug reaction related to cetuximab and found that patients with head and neck cancer were more likely to have infusion reactions and drug related deaths [12] It is unclear whether this side effect is more prevalent in head neck malignancies due to limited number of cases or more frequent reporting by health care professionals because of increased awareness.

Conclusion

Aseptic meningitis is a rare complication of cetuximab which should be recognized in clinical practice. It would be clinically relevant to evaluate the observed higher incidence of aseptic meningitis in head neck cancer compared to NSCLC and colorectal cancer.

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