

Single Case – General Neurology

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# Cetuximab-Induced Aseptic Meningitis in a Patient with Colorectal Cancer: A Case Report and Review of Literature

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## Keywords

Colorectal cancer · Cetuximab · Aseptic meningitis

## Abstract

Cetuximab is a chimeric IgG1 monoclonal antibody against epidermal growth factor receptor. It is approved by the European medical agency for the treatment of RAS wild-type metastatic colorectal cancer and metastatic squamous cell cancer of the head and neck. Few cases of aseptic meningitis, primarily associated with the first administration of cetuximab in patients with squamous cell cancer, have been reported. So far, there was only 1 case in a patient with metastatic colorectal cancer. We report on a 50-year-old Caucasian patient with metastatic rectum carcinoma who suffered from headache, fever, and neck stiffness 3 h after the first administration of cetuximab (400 mg/m<sup>2</sup>). CSF examination revealed an excessive pleocytosis with a white blood cell count of 2,433/μL. He was diagnosed with cetuximab-induced aseptic meningitis since clinical symptoms and CSF pleocytosis resolved within days, and further diagnostic workup revealed no infectious cause. Cetuximab-induced aseptic meningitis is a rare and severe drug reaction with predominance in treating squamous cell cancer of the head and neck. Clinical presentation and CSF findings suggest acute meningoencephalitis. In all reported cases, the course of the disease was benign and self-limited. Empiric antimicrobial and antiviral therapy are suggested until infectious causes can be ruled out. A lower dosage of cetuximab and a premedication including antihistamines and glucocorticosteroids may lower the risk of a re-occurrence if cetuximab therapy is continued.

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## Introduction

Cetuximab is a chimeric IgG1 human/mouse monoclonal antibody against epidermal growth factor receptor. It is approved by the European medical agency for the treatment of metastatic squamous cell cancer of the head and neck and RAS wild-type metastatic colorectal cancer. In the palliative treatment of colorectal cancer, it may be used as a single agent and in combination with radiation therapy and chemotherapy (e.g., FOLFIRI [folinic acid, 5-fluorouracil, irinotecan]) [1, 2].

So far, few cases of aseptic meningitis associated with cetuximab application have been reported (see Table 1). Our MEDLINE analysis showed that most cases were associated with the first administration of cetuximab in patients with squamous cell cancer. Here, a higher dose (400 mg/m<sup>2</sup>) is administered, while in consecutive administrations, 250 mg/m<sup>2</sup> is recommended. One case of aseptic meningitis was found in a patient with metastatic colorectal cancer after the 12th administration of cetuximab at the lower dosage (250 mg/m<sup>2</sup>) [3]. Even if clinical symptoms and CSF findings suggest severe bacterial meningitis, the course of cetuximab-induced aseptic meningitis is benign and self-limited within a few days.

## Case Report

We present a 50-year-old Caucasian man with metastatic rectum carcinoma. As first-line treatment, the patient was treated by low anterior resection and atypical liver resection of segments 4b/5. After R2 resection due to multiple bilobular hepatic filiae, a palliative first-line treatment was started. After determination of all RAS wild type within the IVOPAK II-study [4], the patient was offered weekly cetuximab in combination with FOLFIRI biweekly, following the dosing regimen of Van Cutsem et al. [5]. Before the first administration of cetuximab, 2 mg of clemastine iv was administered, following the usual protocol. No glucocorticosteroids were given. Hereafter, 860 mg cetuximab (400 mg/m<sup>2</sup>) was administered intravenously within 2 h. The patient presented no adverse side effects besides a mild flush during administration. Afterwards, he received an infusion of isotonic saline and was monitored for another hour. Then he was discharged without any clinical symptoms. However, 2 h later, the patient developed a severe headache, neck stiffness, and fever with a tympanic temperature of 39°. He immediately presented to our neurological emergency department.

Clinical examination revealed no focal neurological deficit. Cerebrospinal fluid (CSF) analysis revealed a severe polymorphonuclear neutrophil-predominant pleocytosis (87.8%) with a white blood cell (WBC) count of 2,433/μL. Further laboratory testing (including complete blood count, coagulation profile, and a comprehensive metabolic panel) remained unremarkable. Empirical broad-spectrum treatment was initiated, including ceftriaxone, ampicillin, aciclovir, and dexamethasone. He recovered from headaches, neck stiffness, and fever within 2 days. After 5 days, a repeated CSF analysis showed a complete recovery. After extensive viral and bacterial diagnostic workup (including assessment of herpes simplex type 1 and 2 [PCR], varicella zoster [PCR], human herpesvirus 6 and human herpesvirus 7, Epstein-Barr virus, cytomegalovirus, adenovirus, tick-borne encephalitis virus, *Borrelia burgdorferi*, *Treponema pallidum*, CSF cytology, and CSF culture/staining [bacterial and fungal]) remained unremarkable, antibiotic and antiviral therapy was discontinued. The patient and treating physicians decided to terminate the cetuximab treatment in a joint decision.

To estimate the probability of an adverse drug reaction (ADR), in this case, the Naranjo Score was applied. Following Naranjo et al. [6], the estimated probability for an ADR, in this case, was considered “probable” (Naranjo Score: 5, see Table 2).

**Table 1.** Published cases of cetuximab-associated aseptic meningitis in patients with squamous cell cancer of the head and neck and colorectal cancer

Case	Study	Age, sex	Diagnosis	Dose of cetuximab	Symptoms	Onset	CSF findings	Treatment and course (if specified)	CSF follow-up	Cetuximab re-challenge	Recurrence of meningial irritation
1 (phase-I study)	[7]	NR	NR	100 mg/m <sup>2</sup> (third dose); no premedication with glucocorticoids and antihistaminic drug reported	Grade 3 aseptic meningitis	NR	NR	NR	NR	No	-
2	[8]	45 years, m	Locally recurrent laryngeal squamous cell carcinoma	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Frontal headache, fever (38.8°C)	A few hours after administration	WBC 2,300/μL, 98% neutrophils, protein 1.04 g/L, normal glucose	Ceftriaxone, vancomycin, ampicillin, aciclovir	Resolution of neutrophilic pleocytosis and protein level	A week later, dose: 250 mg/m <sup>2</sup> ; premedication: dexamethasone	No
3	[8]	42 years, m	Locally advanced squamous cell carcinoma of the right tonsil	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Frontal headache, fever (39.4°C)	8 h after administration	WBC 2,267/μL, 90% neutrophils, protein 1.46 g/L, normal glucose	Ceftriaxone, vancomycin, ampicillin, acyclovir, dexamethasone; prolonged meningial symptoms lasting for 12 days	WBC 0/μL, protein 0.69 g/L	Two weeks later; dose: 250 mg/m <sup>2</sup> ; premedication: dexamethasone	No
4	[9]	78 years, f	Stage 3A NSCLC	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids reported	Frontal and occipital headache, nausea, vomiting, neck stiffness	A few hours after administration	WBC 459/μL, 89% neutrophils, protein modestly elevated, normal glucose	Broad-spectrum antibiotics	NR	Dose: 250 mg/m <sup>2</sup> ; premedication: steroids	No
5	[9]	59 years, m	Metastatic NSCLC	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids reported	Acute encephalopathy	A few hours after administration	WBC 302/μL, 97% neutrophils, protein 1.16 g/L, glucose 2.83 mmol/L	Broad-spectrum antibiotics; symptoms resolved within "several days"	NR	Dose: 250 mg/m <sup>2</sup> ; premedication: steroids	No
6	[10]	54 years, f	Stage 4B squamous maxillary cancer with metastatic right lymph node	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Frontal headache, neck discomfort, fever (39.9°C)	A few hours after administration	WBC 1,025/μL, 92% neutrophils, protein 1.65 g/L, normal glucose	Ampicillin, vancomycin, cefepime	NR	Weekly, 250 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids reported	Yes, after 1 month (WBC 715/μL)
7	[12]	67 years, m	Recurrent advanced oropharyngeal squamous cell carcinoma	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids reported	Headache, fever (39.2°C), psychomotor slowing	9 h after first administration	WBC 1,413/μL, 92% neutrophils, protein 1.78 g/L, glucose 3.5 mmol/L, lactate 3.0 mmol/L	Cefazidim, vancomycin, amoxicillin, and aciclovir plus dexamethasone; symptoms resolved within 14 days	WBC 1/μL, protein 0.68 g/L, glucose 4.0 mmol/L, lactate 1.5 mmol/L	No	-

Table 1 (continued)

Case	Study	Age, sex	Diagnosis	Dose of cetuximab	Symptoms	Onset	CSF findings	Treatment and course (if specified)	CSF follow-up	Cetuximab re-challenge	Recurrence of meningeal irritation
8	[11]	58 years, m	Tonsillar squamous cell cancer	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Headache, fever (38.9°C)	1 h after first administration	WBC 473/μL, 80% neutrophils, protein 1.28 g/L, glucose 3.66 mmol/L	Vancomycin, ceftriaxone, ampicillin, dexamethasone; symptoms improved by day 2	NR	With 250 mg/m <sup>2</sup> after 7 days; no premedication with glucocorticosteroids reported	No
9	[1]	66 years, f	Stage 4A locally advanced laryngeal squamous cell carcinoma	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Headache, photophobia, neck stiffness, vomiting, no fever	4 h after administration	WBC 4,100/μL, 90% neutrophils, protein 1.5 g/L, glucose 3.16 mmol/L	Ceftriaxone; symptom resolution was reported by day 2	NR	With 250 mg/m <sup>2</sup> after 28 days; premedication: methylprednisolone 80 mg i.v.	No
10	[13]	65 years, f	Laryngeal cancer	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Photophobia, headache, neck stiffness, fever (39.4°C)	6 h after administration	WBC 321/μL, 91% neutrophils, protein 1.12 g/L, glucose 2.66 mmol/L, lactate NA	"Broad-spectrum antibiotics"; symptoms improved on day 3	NR	After 2 weeks, 250 mg/m <sup>2</sup> ; premedication: 12 mg dexamethasone	No
11	[3]	43 years, f	Metastatic colon cancer	250 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids reported	Headache, nausea, vomiting, neck stiffness, photophobia, febrile temperature	9 h after administration	WBC 2,953/μL, 95% neutrophils, protein 1.43 g/L, glucose "normal," lactate NA	Meropenem, acyclovir, ampicillin; symptoms resolved on day 4	NR	No	-
12	Current case	50 years, m	Metastatic rectum carcinoma	400 mg/m <sup>2</sup> ; no premedication with glucocorticosteroids	Headache, neck stiffness and fever up to 39°C	3 h after administration	WBC 2,433/μL, 87% neutrophils, protein 1.01 g/L, glucose 4.1 mmol/L, lactate 4.35 mmol/L	Ceftriaxone, ampicillin, acyclovir, dexamethasone; symptoms resolved within 48 h	WBC 10/μL	No	-

A premedication with an antihistaminic drug was reported in all cases before cetuximab application except in case 1 (phase-I study). y, year; m, male; f, female; NR, not reported; NA, not available; CSF, cerebrospinal fluid; WBC, white blood cell; NSCLC, non-small cell lung cancer.

**Table 2.** ADR probability scale – Naranjo Score. To assess the probability of an ADR, following questionnaire was applied

Question	Yes	No	Do not know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	<b>+1</b>	0	0	<b>+1</b>
2. Did the adverse event appear after the suspected drug was administered?	<b>+2</b>	-1	0	<b>+2</b>
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	<b>0</b>	0	<b>0</b>
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	<b>0</b>	<b>0</b>
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	<b>+2</b>	0	<b>+2</b>
6. Did the reaction reappear when a placebo was given?	-1	+1	<b>0</b>	<b>0</b>
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	<b>0</b>	<b>0</b>
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	<b>0</b>	<b>0</b>
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	<b>0</b>	<b>0</b>
10. Was the adverse event confirmed by any objective evidence?	+1	0	<b>0</b>	<b>0</b>
				<b>Total score +5</b>

ADR, adverse drug reaction.

Cut-off points include the following: ≤0 doubtful ADR; 1–4 possible ADR; 5–8 probable ADR; ≥9 definite ADR.

Interpretation: following Naranjo Score, the estimated probability of an ADR was considered as “probable” in this case.

## Discussion

We report on a case of clinically pronounced aseptic meningitis within hours after the first cetuximab treatment with a dosage of 400 mg/m<sup>2</sup> in a patient with metastatic colorectal cancer, followed by fast and full recovery within 2 days. So far, few cases of aseptic meningitis related to a previous administration of cetuximab have been reported (see Table 1) [1, 3, 7–13].

Most patients showed mild clinical symptoms with headache and fever. However, some cases also reported encephalopathy and psychomotor slowing [9, 12]. CSF WBC count was elevated with a neutrophil-predominant cell profile (range: 302–4,100 WBC/μL) in all cases, which corresponds well to our case. So far, no associated bacterial superinfection was reported. In general, clinical symptoms occurred between one and 9 h after the administration of cetuximab. Most cases were reported in patients with squamous cell carcinoma of the head and neck after the first cetuximab application with a dosage of 400 mg/m<sup>2</sup>. Several studies on cetuximab application in colorectal cancer did not report aseptic meningitis as an adverse event [14–17]. The only reported case of aseptic meningitis in a patient with metastatic colon cancer was associated with the lower dose of 250 mg/m<sup>2</sup>. In contrast to all other reported cases, aseptic meningitis occurred after the 12th administration of cetuximab [3]. No premedication with glucocorticoids was reported before the respective cetuximab application (see Table 1). A timely standard empiric antimicrobial and antiviral therapy are suggested until an infectious cause is ruled out. All cases showed a self-limited course with complete recovery, irrespective of whether dexamethasone was added to the antimicrobial treatment. In six of the reported cases (50%), cetuximab was reintroduced at a lower dosage (250 mg/m<sup>2</sup>) after aseptic meningitis. Furthermore, a premedication with

glucocorticosteroids was added before the consecutive cetuximab applications in all but 2 cases. In one of those 2 cases, there was a recurrence of aseptic meningitis within 4 weeks, showing a benign course [10]. In our case, the decision was made to discontinue the treatment with cetuximab to prevent further events of ADRs. FOLFIRI was continued.

The pathophysiological background of this rare adverse event remains unclear. However, it seems that aseptic meningitis is mainly related to the following three (risk) factors. (1) A higher dose of cetuximab is suggested as the first administration dose (initial dose 400 mg/m<sup>2</sup> vs. subsequent dose 250 mg/m<sup>2</sup>) in the treatment of metastatic squamous cell carcinoma of the head and neck and metastatic colon carcinoma [1]; however, since there is only 1 case reported in metastatic colon carcinoma, it remains to be elucidated whether the dose-dependent risk also exists in patients with colorectal cancer. Furthermore, a clear association of symptom duration with cetuximab half-life (approx. 112 h) can also not be concluded from existing data since most patients seem to recover within 48–96 h (see Table 1) after symptom onset. (2) The application of cetuximab in squamous cell cancer of the head and neck; (3) a premedication without glucocorticosteroids. Interestingly, panitumumab, a human IgG2 monoclonal antibody against epidermal growth factor receptor, was not reported to be associated with aseptic meningitis [18]. This might support the etiological hypothesis of an inflammatory response related to the chimeric (mouse/human) nature of cetuximab in terms of an antibody-dependent cell cytotoxicity effect [19]. In general, most of the above associations suggest an inflammatory response comparable to an allergic hypersensitivity reaction due to cetuximab antibodies crossing the blood-brain barrier [1, 13]. Comparable pathomechanisms have been reported in aseptic meningitis associated with intravenous immunoglobulin therapy [20]. Here, also dose-dependent effects have been described [21]. While some debate is still ongoing on whether a monoclonal antibody like cetuximab may be able to cross the blood-brain barrier due to its biochemical size; other reports describe a CSF antibody detection in a comparable setting [22] with a possible inflammatory reaction [23] affecting the CNS. Furthermore, the association of aseptic meningitis with cetuximab administration in squamous cell cancer of the head and neck, which in turn might be associated with certain virus infections, might also suggest a distinct inflammatory response [24]. Some authors suggest an involvement of interleukins in antibody-associated aseptic meningitis. An example may be the involvement of the interleukin-6 (IL-6) pathway, which was shown to be associated with aseptic meningitis related to the anti-IL-6-receptor antibody tocilizumab [25]. Interleukins may also play a role in tumor-associated processes of squamous cell carcinomas of the head and neck [26]. Furthermore, an association of IL-6-gene activation with the cetuximab-induced acneiform rash has been described in the treatment of squamous cell carcinoma of the head and neck, which is also supposed as a biomarker of the immunological response to cetuximab and related processes [19]. Thus, one may hypothetically propose an association of cytokine activation with cetuximab-associated aseptic meningitis. However, this could not be proven so far in this setting.

An inflammatory response seems likely in patients with aseptic meningitis after cetuximab administration. The risk of re-occurrence is generally low, especially if a lower cetuximab dosage is administered and a premedication with glucocorticosteroids is added. Thus, an anti-inflammatory premedication (including glucocorticosteroids) is proposed. However, pathophysiological mechanisms still need to be elucidated.

## Conclusion

Cetuximab-associated aseptic meningitis is a rare side effect with a benign course despite pronounced initial symptoms and CSF findings. Nevertheless, immediate empiric antimicrobial and antiviral therapy are suggested until infectious causes are ruled out. A lower dose of

cetuximab (250 mg/m<sup>2</sup>) and a premedication including glucocorticosteroids may be associated with a low risk of a re-occurrence of aseptic meningitis if cetuximab therapy is continued. Panitumumab may also represent a promising alternative treatment option since no aseptic meningitis associated with panitumumab treatment has been reported so far.

### Statement of Ethics

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided his written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Bastian Volbers and Jakob Jäger: design of the work and drafting the manuscript. Axel Wein, Francesco Vitali, and Martin Uhl: acquisition of data and critical revision of the article for important intellectual content. Stefan Schwab, Tamara Brunner, and Maximilian Sprügel: interpretation of data and critical revision of the article for important intellectual content. Jakob Jäger, Maximilian Sprügel, Tamara Brunner, Martin Uhl, Stefan Schwab, Francesco Vitali, Axel Wein, and Bastian Volbers approved the final version.

### Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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