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**Case Report**

# Capecitabine-Related Fourth Nerve Palsy: A Case Report

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**Keywords**
Capecitabine · Palsy · Neurotoxicity

**Abstract**
***Introduction:*** Capecitabine has rarely been associated with neurotoxicity. Cerebellar ataxia, multifocal leukoencephalopathy, and sensorimotor peripheral neuropathy have been reported in the literature. A case of 6th nerve palsy associated with capecitabine has also been described. This article reports the first case of capecitabine-related 4th nerve palsy. ***Case Presentation:*** A 72-year-old Caucasian woman was referred by the Oncology Department because she had been complaining of binocular diplopia for 6 months. The symptoms started 1 month after the introduction of capecitabine. A diagnosis of right 4th nerve palsy was made using the Parks three-step test and the Hess test. Neuroimaging analysis was negative. A slow but progressive deterioration of function was confirmed during a year of follow-up. On suspicion of a chemotherapy-related palsy, capecitabine was discontinued and switched to vinorelbine. Subsequent improvement of the clinical picture was confirmed within 2 months. ***Conclusion:*** The recognition of chemotherapy-related neurotoxicity is of paramount importance in the management of oncology patients. Once secondary invasion of the brain or the orbit by the tumor itself is ruled out, it must be suspected to prevent further deterioration.



## Introduction

Capecitabine is a chemotherapeutic drug that acts as an antimetabolite. It is used in the treatment of breast, esophageal, gastric, colon, rectal, and pancreatic cancers. Notably, it is effective in the treatment of metastatic breast tumors and triple-negative forms with residual

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invasive disease after standard neoadjuvant chemotherapy [1]. Capecitabine treatment has rarely been associated with neurotoxicity. We report the first case of capecitabine-related 4th nerve palsy.

## Case Report

A 72-year-old Caucasian woman was referred by the Oncology Department because she had been complaining of binocular diplopia for 6 months. The patient was diagnosed with HER2-negative breast cancer in 2010. In 2015, progression to stage IV disease with lung, lymph nodes, and spine involvement occurred. Chemotherapy was started, and she was switched to capecitabine in October 2021 with a gradual increase in dose. After 1 month, the patient began to complain of diplopia. She was examined by an ophthalmologist with no abnormal findings. However, the symptoms progressively worsened, so a second ophthalmologist's opinion was asked. On this examination, her previous ophthalmologic history was unremarkable. Her best-corrected visual acuity was 20/20 in both eyes. Pupillary examination showed no defect. Anterior segment and dilated fundus examinations were normal. She reported diplopia in primary gaze, worse in downgaze, lasting from 6 months. An ocular motility exam showed right hypertropia in the primary position, increasing in left gaze. She showed a tendency to depress her chin. The Parks three-step test and Hess test (shown in Fig. 1a) were consistent with right 4th nerve palsy. Lids' position and movement observations revealed no abnormalities; the presence of proptosis and orbicularis strength weakness were also excluded. A neurological consultation was asked, which revealed no other positive findings. Contrast computed tomography of the brain and orbit was performed, and any space-occupying lesion was detected (shown in Fig. 2). The images were also compared with a previous examination executed in 2016 with no difference. Magnetic resonance neurography was thus advised, but the patient refused due to claustrophobia. In the hypothesis of a microischemic nature, a monthly clinical observation was thus scheduled. However, the expected improvement of the clinical picture did not occur, making this origin improbable. Over the next year, subjective symptoms intensified, consistent with a slow but progressive deterioration of function as recorded in consecutive Hess tests (shown in Fig. 1b). Systemic risk factors such as hypertension and diabetes were excluded. During this period, serum tumor marker analysis and 18F-FDG PET/CT were also performed for disease monitoring as scheduled by her oncologist. After an initial good response, CEA and CA 15.3 showed a slight but gradual increase after 1 year, which was accompanied by a mild radiological progression of skeletal lesions. Given the onset of diplopia after capecitabine administration, chemotherapy-related 4th nerve palsy was suspected. The oncologist was informed. Capecitabine was discontinued, and it was switched to vinorelbine, with subsequent improvement of the clinical picture within 2 months (shown in Fig. 1c). PET/CT re-evaluation at 6 months showed disease stability.

## Discussion

Capecitabine is a 5-fluorouracil prodrug. Neurotoxicity is a rare side effect of 5-fluorouracil therapy, while it is infrequently reported after capecitabine administration [2, 3]. Cerebellar ataxia and multifocal leukoencephalopathy have been described in the literature [4]. Two cases of sensorimotor peripheral neuropathy have also been reported, confirmed by electromyogram and nerve conduction studies [5]. The first patient developed right leg weakness during the 4th week of treatment, which resolved after 1-month treatment

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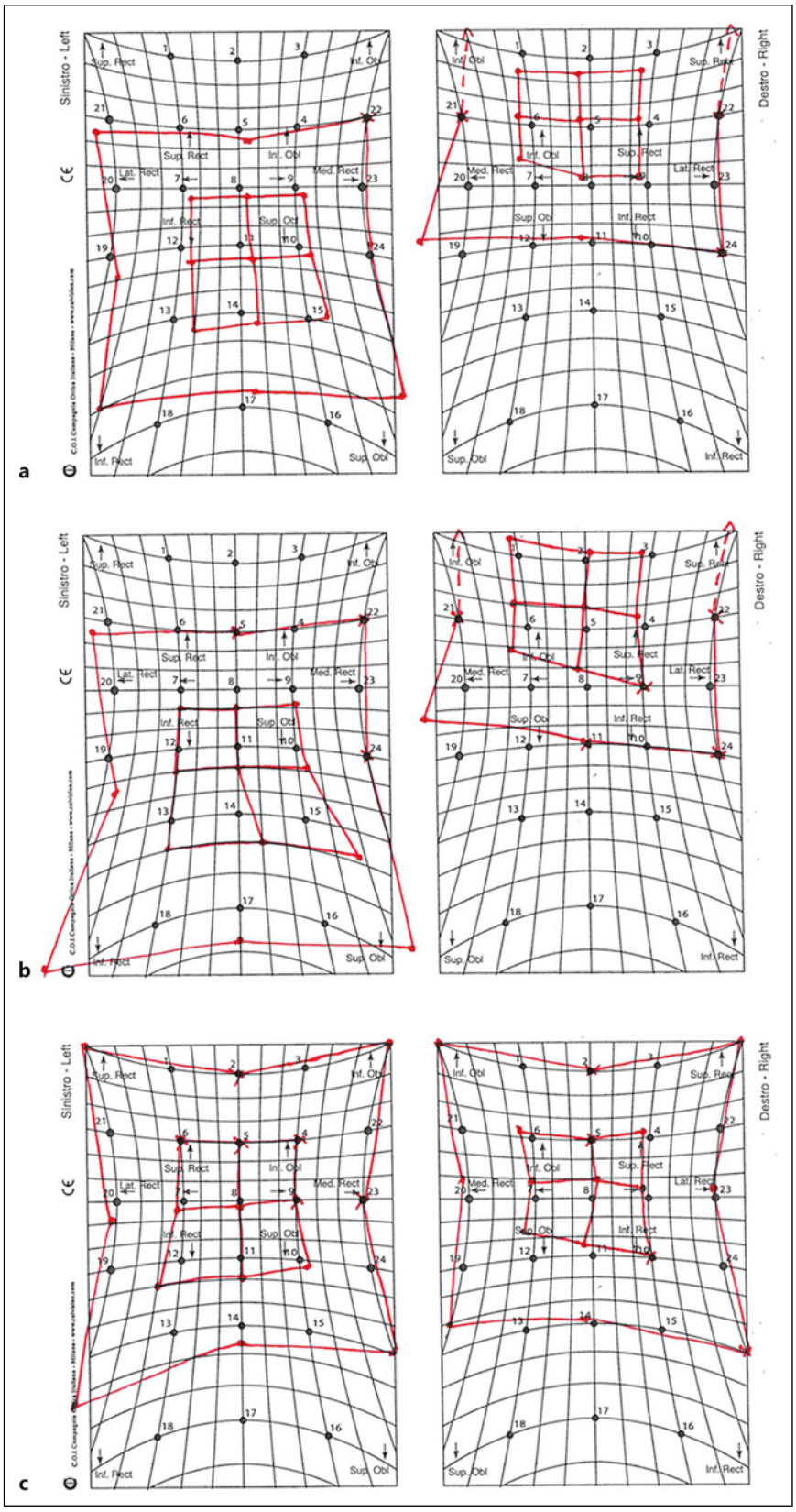


**Fig. 1.** Consecutive Hess tests showing the course of the right 4th nerve palsy. The palsy at initial evaluation (**a**), worsening over 1 year (**b**), improvement 2 months after capecitabine discontinuation (**c**).

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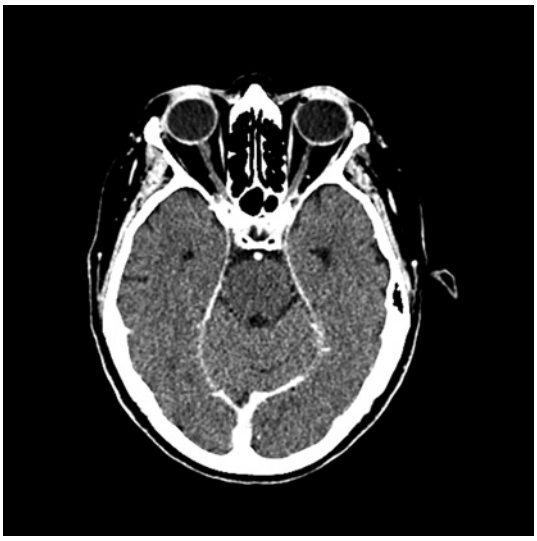

**Fig. 2.** Brain and orbit contrast computed tomography. Any space-occupying lesion was detected.

interruption and did not recur after treatment resumption. The second patient manifested perioral and upper extremity paresthesia after 5 months of therapy. The standard dose was reduced by 20% with symptom resolution. Capecitabine-induced 6th nerve palsy was also described in the literature: symptoms appeared 3 days after the start of treatment and gradually disappeared during the following month after capecitabine was withdrawn [6]. In our case, diplopia developed 1 month after the introduction of capecitabine. A micro-ischemic nature was excluded due to the gradual worsening of symptoms in almost 1 year of clinical monitoring. Improvement was observed after the discontinuation of capecitabine. Magnetic resonance neurography could not be performed, so a definite diagnosis could not be made, leaving the possibility of alternative etiology open. However, the correlation between the start of the use of capecitabine and the course of the clinical picture suggests that the drug may be the culprit in this case. Binocular diplopia can harbor serious pathologies, especially in cancer patients. Moreover, it represents a debilitating symptom, which can further affect their quality of life. According to Çelik et al., the most common etiology of strabismus in cancer patients is represented by orbital or brain metastasis or local invasion [7]. More rarely, it can occur secondary to radiotherapy and chemotherapy. The recognition of chemotherapy-related neurotoxicity is of paramount importance in the management of oncology patients. Once secondary invasion of the brain or the orbit by the tumor itself has been excluded, it must be suspected to avoid further deterioration. The underlying etiology of capecitabine neurotoxicity remains not understood. Future research investigating other pathogenic pharmacogenetic processes is required to further elucidate these associations.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535349).

## Statement of Ethics

This study protocol was reviewed and approved by Ethic Committee of the University of Trieste, approval number 87/23. Written informed consent was obtained from participant for publication of the details of her medical case and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

Data analysis and interpretation: M.R.P. Manuscript writing: M.R.P. and S.M. Manuscript editing and approval: M.R.P., S.M., G.C., and D.T.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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