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Capecitabine-induced oromandibular dystonia: A case report and literature review

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We report a rare case of capecitabine-induced oromandibular dystonia and a summary of the cases reported in the literature.

A 57-year-old Chinese male was diagnosed with a pT3N2 stenosing adenocarcinoma of the rectum in January 2007, for which he underwent a low anterior resection. During staging evaluation, he was found to have a subcentimetre segment 2 liver lesion which was confirmed to be a solitary liver metastasis on positron emission tomography (PET). The plan was to give him two cycles of "neoadjuvant" capecitabine and oxaliplatin given every 3 weeks before resection of the liver metastasis, followed by further chemotherapy and radiotherapy. He was started on cycle 1 of capecitabine 2500 mg/m^2 (days 1–14) and oxaliplatin 130 mg/m^2 (day 1) on February 9, 2007.

Nine days after consuming capecitabine he developed sudden onset of disability to talk and swallow. Clinical examination revealed he had dystonia of tongue and pharyngeal muscles as well as involuntary jaw clenching. He did not have any other focal neurological signs nor associated metabolic abnormalities. He did complain of fatigue and anorexia but did not have features of hand-foot syndrome, haematological nor gastrointestinal toxicities.

Computer tomography of his brain done on the same day showed no obvious abnormalities. However, a magnetic resonance imaging (MRI) scan was done which showed non-enhancing abnormalities with restricted diffusion involving bilateral corona radiate, the centrum semiovale and splenium of corpus collosum with scattered brainstem lesions noted (Figures 1 and 2) consistent with multifocal leukoencephalopathy.

Capecitabine was discontinued on admission. A feeding tube had to be inserted as he had difficulty swallowing and he required a writing board to communicate. After 3 days, his symptoms completely resolved. Blood taken from the patient was analysed for TS 5′ gene polymorphisms and showed class 3 (3RG/3RC) genotype.

He was switched to raltitrexed and oxaliplatin as further therapy and no further neurological events occurred. A repeat MRI of his brain was done on March 20, 2007 (Figure 3), which showed significant improvement in the periventricular leukoencephalopathy. He underwent an uneventful liver resection on April 17, 2007 and remains neurologically asymptomatic.

Capecitabine is a proven oral chemotherapy agent in breast and colorectal cancer, which is increasingly

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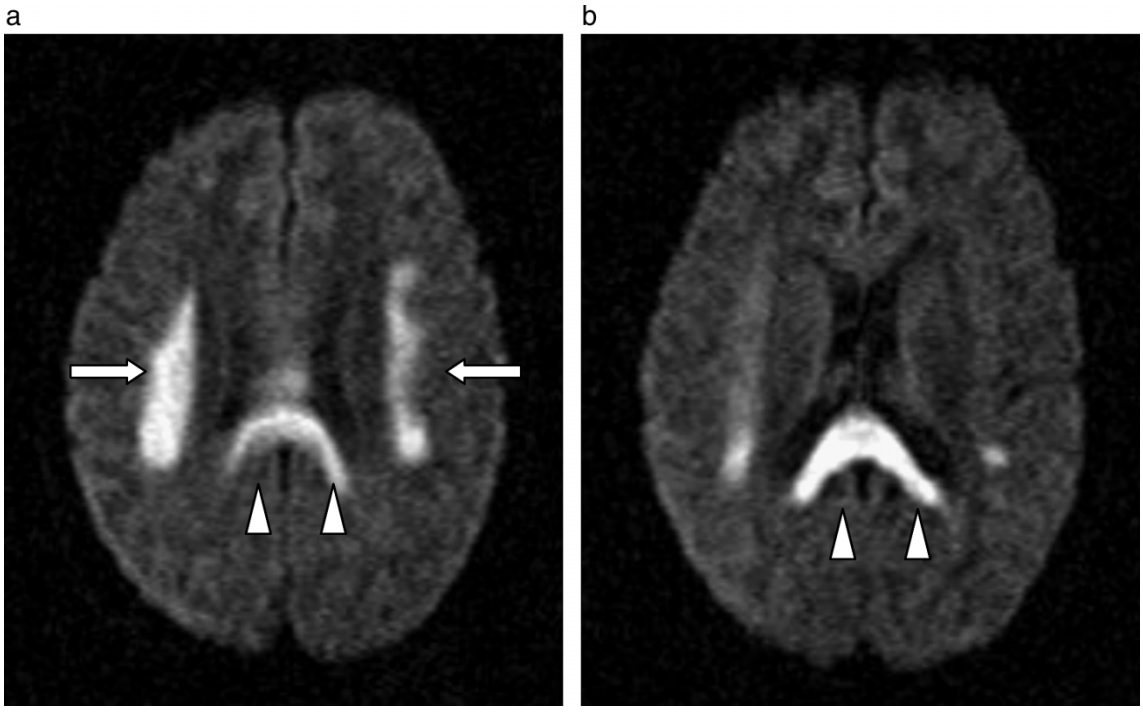

Figure 1a & b.

used due to its ease of administration. Its antineoplastic activity is related to its final conversion to 5-fluoruracil (5FU). Side effects of capecitabine appear to be similar to those seen in 5FU treated patients, but with a more favourable profile [1]. Capecitabine is a fluoropyrimidine carbonate which is rapidly absorbed and metabolized in the liver to 5′deoxy-5 flurocytidine (5′-DFCR) and then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytamine deaminase, The final step exploits higher

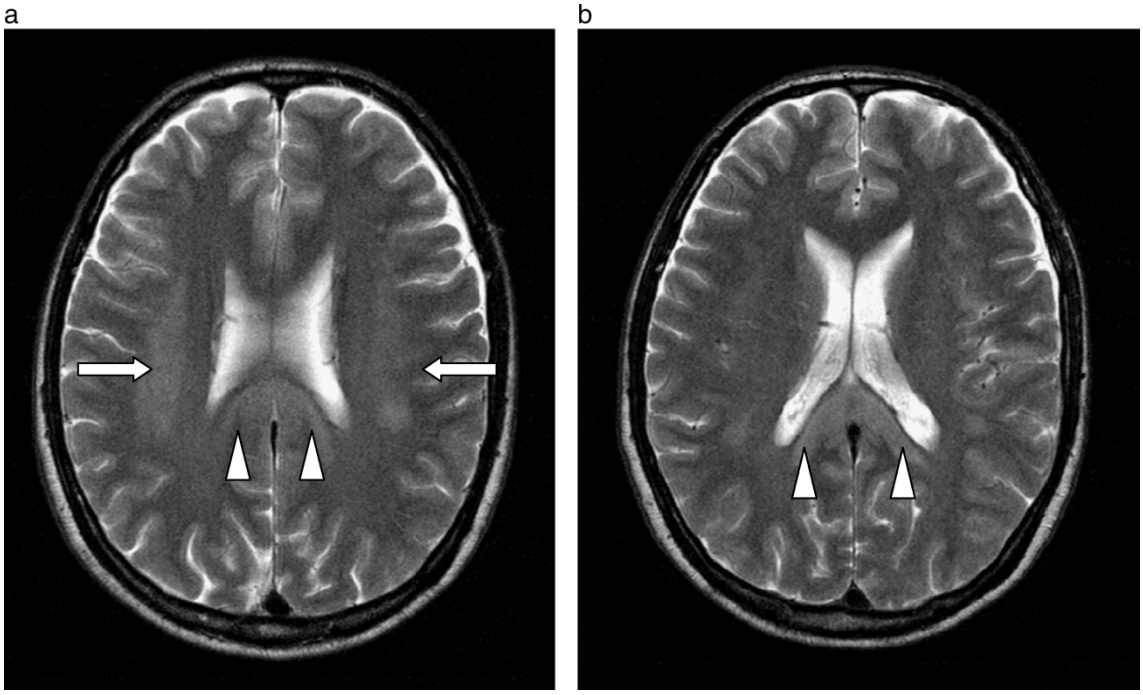

Figure 2a & b. Axial diffusion- (Figure 1a & b) and T2- (Figure 2a & b) weighted images showing restricted diffusion and T2 signal hyperintensity involving the corona radiata (arrows) and splenium of the corpus callosum (arrowheads) in a symmetrical manner at initial presentation.

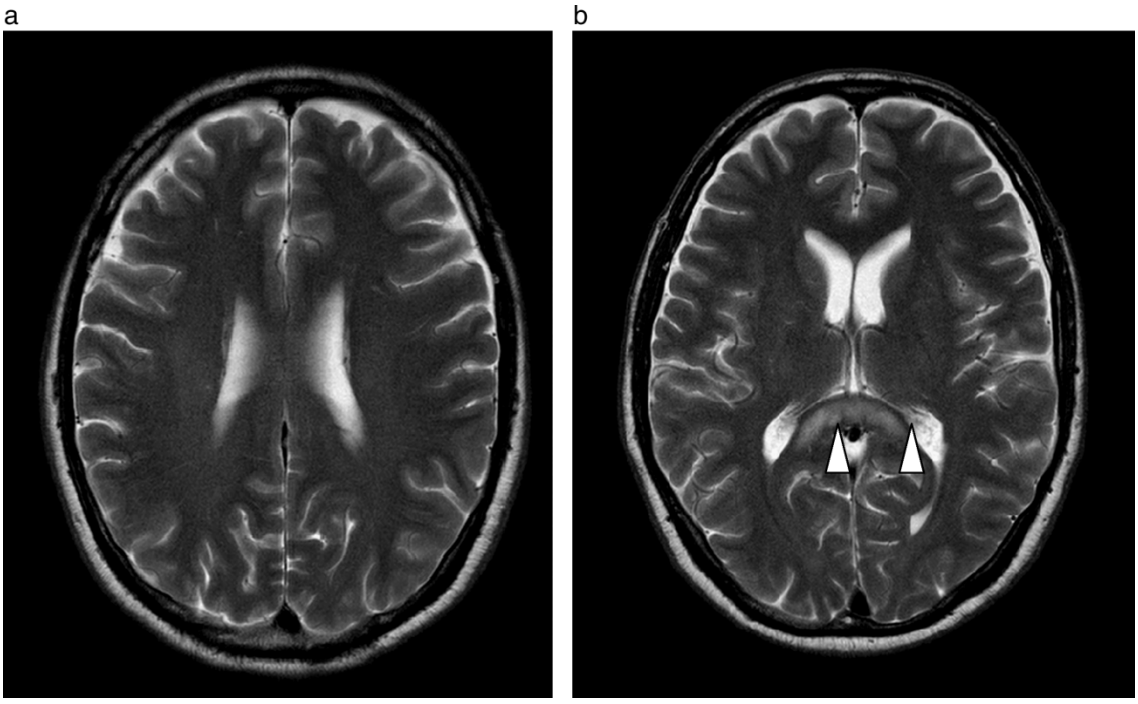

Figure 3a & b. Follow-up MR study performed a month later shows resolution of the previously noted T2W signal hyperintensity in the corona radiata with some residual T2W signal hyperintensity seen in the splenium of the corpus callosum (arrowheads).

concentrations of thymidine phosphorylase in tumour tissue which reduces 5′-DFUR to 5-fluotouracil (5-FU). Thus, the drug is selectively activated in the tumour and systemic toxicity is lessened [2].

Here, we report a rare case of capecitabine-induced oromandibular dystonia without any other associated neurological signs, presenting 9 days after initiating treatment. Unlike 5FU, there have been few reports of capecitabine-induced central neurotoxicity and its incidence is estimated as less than 0.5% [2]. Previous cases have reported symptoms of ataxia, cognitive changes, dysathria, epilepsy-like symptoms and even coma (see Table I) [3–6] but not oromandibular dystonia alone. Onset of neurological symptoms occurred early within 3–7 days of initiating capecitabine therapy unlike neurotoxicity associated with 5FU which can occur later [7]. Similar to previous reports, MRI of our patient's brain revealed white matter changes consistent with periventricular leukoencephalopathy and these changes resolved spontaneously together with the clinical symptoms, on termination of capecitabine therapy. These changes on imaging are also seen in 5FU-related leukoencephalopathy [8,9]. Though, 5FU-encephalopathy has also been associated with an inflammatory leukoencephalopathy which has a delayed onset and recovery [10].

While the actual mechanistic reason for leukoencephalopathy in both capecitabine or 5FU use is poorly understood. Severe neurotoxicity from 5FU has been associated with dihydropyrimidine dehydrogenase deficiency (DPD) and it has been postulated that a DNA-directed or thymidylate synthase-based mechanism is the underlying event, thus making infusional thymidine a therapeutic option for patients with this toxicity [11]. Small studies have also correlated DPD deficiency with capecitabine toxicity [12] though not central neurotoxicity in particular. A trend toward a higher global toxicity grade 3 and 4 has been observed in patient's homozygous (class 4 genotype) for the TS 3RG allele compared with patient's heterozygous for the 3RG allele or not carrying the 3RG allele [12]. Our patient was not assessed for DPD deficiency but was heterozygous for the 3RG allele.

Central toxicity in the absence of brain metastases may well indicate that capecitabine and its compounds can pass through the blood brain barrier (BBB). Capecitabine has also been shown to effectively cause regression of brain metastases [13] though it is difficult to rule out the tumour-induced alterations in the BBB as a contributing factor. Nucleosides (like capecitabine metabolites 5′-DFCR and 5′ –DFUR) have been shown to be transported through the BBB by *in vivo* brain uptake index (BUI) and brain transfusion methods as well as *in vitro* isolated capillary and cultured endothelial cells [14] and there is some evidence that 5FU itself may diffuse across the BBB too [13]. The capecitabine metabolite, 5-DFUR, but not capecitabine

Table I. Summary of case reports on capecitabine-induced multifocal leukoencephalopathy.

Case report	Year of report	No of patients	Clinical manifestations	Median onset of neurological s ymptoms (day)	MRI findings	Outcome
Couch LS et al.[3]	2003	1	Painful trismus and left sided neglect	Day 2	Diffuse white matter hyperintensity	Complete resolution of symptoms
Niemann et al.[4]	2005	1	Painful spasms of throat and manidibular muscles ('epilepsy-like symptoms')	Day 6	Diffuse subcortical white matter alterations	Complete clinical and pathological recovery
Formica et al.[5]	2005	1	Ataxia and jerking movements of extremities; progressed to coma	Day 7	Non-specific minimal low attenuation white matter	Complete recovery
Videnovic et al.[6]	2005	5	Ataxia, headaches, short-term memory loss, confusion, vertigo, dysarthria and epilespy-like symptoms	Days 3–7	Increased signal on DWI, fluid attentuated, T2 sequences in areas of corpus callosum, brachium pontis and deep perventricular matter	All complete recovery/ minimal residual deficits

itself or 5FU is transported via a substrate pyrimidine preferring transporter, hCNT1. Expression of this transporter promotes increased sensitivity of this prodrug and may thus determine cytoxicity of capecitabine [15,16].

In summary, we present an unusual case report of capecitabine-induced oromandibular dystonia which had MRI and complete clinical resolution after discontinuation of the drug. As capecitabine usage increases, a better understanding of pharmacogenetics may shed light on mechanisms of capecitabine neurotoxicity. In the meantime, awareness among clinicians about this reversible chemotherapy adverse effect will avoid delay in diagnosis and management.

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FDG-PET for a thyroid MALT lymphoma

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To the Editor

We previously reported on a patient in this journal (Acta Oncol 2006;45:750–2) who had a gastric mucosa-associated lymphoid tissue (MALT) lymphoma (MALToma) which showed intense F-18-fluoro-deoxyglucose (FDG) uptake into the tumor [1]. FDG positron emission tomography (PET) has been considered the first-line modality for staging, restaging, and monitoring the therapeutic response for lymphomas. However, variable FDG avidity in MALTomas has been reported in the literature, and the usefulness of this modality for MALTomas is controversial [2–4]. A recent report suggested that a MALToma with plasmacytic differentiation may be related to FDG uptake [5]. We recently had a patient with an invasive thyroid MALToma which showed intense FDG uptake in the postoperative residual tumor.

A 77-year-old female received a total thyroidectomy for a large, rapidly growing mass in her left thyroid. The operative findings revealed that the mass was elastic and firm with an ill-defined margin and local invasion to the surrounding muscle and vessels. Incomplete removal of the tumor was noted during the operation. Gross pathological findings showed that the specimen was diffusely fibrotic and there was an ill-defined grayish-white tumor in the upper left thyroid. Histopathology revealed an invasive MALT lymphoma in the tumor associated with chronic thyroiditis and fibrosis. Immunohistochemical stains were positive for CD 20, negative for CD5, cyclin D1, CD10 and CD3, which excluded the possibility of other small B-cell lymphomas and follicular cell lymphoma. The cytokeratin stain enhanced the presence of lymphoepithelial lesion. The origin of the neoplastic lymphoid tissue turned out to be marginal zone B cell lymphoma (MALToma). In addition, the tumor had invaded the perithyroidial soft tissue and nerve (Figure 1). Two months after the operation, a whole-body FDG-PET study showed focally intense FDG uptake in the anterior aspect of the left side of the neck, suggestive of a viable residual tissue (Figure 2).

A thyroid lymphoma is a rare, heterogeneous disease comprising approximately $1 \sim 5\%$ of all thyroid malignancies and $1 \sim 2.5\%$ of all lymphomas [6]. Pathogenically, the acquired lymphoid tissue from autoimmune thyroiditis might evolve to MALT and even transform to an aggressive lymphoma in the thyroid [7–10]. Derringer et al. reported that among 108 cases of primary thyroid lymphomas, MALT was identified in 66 cases (61%), including mixed diffuse large B cell lymphoma (DLBCL) with MALT in 36 cases. In addition, lymphocytic

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