To the Editor

Re: Del Brutto O.H. A Review of Cases of Human Cysticercosis in Canada. Can J Neurol Sci. 2012;39:319-22.

Sir, the recent report on cysticercosis in Canada is quite interesting[1]. Del Brutto et al concluded that "the prevalence of this parasitic disease may be on the rise[1]"and mentioned the importance of immigrants who might carry diseases. Indeed, due to rising number of immigrants, the similar situation is also described in Europe[2]. There are many considerations on this report. First, this disease does not directly spread from person to person. Cysticercosis occurs due to intake of contaminated food. The course of disease is usually long. Before overt clinical presentation as neurocysticercosis, silent infestation can be persistent for a long time. The possibility of getting disease in Canada is still questionable. If it is an actual case, it implies a food hygienic problem since the main mode of getting cysticercosis is food-borne transmission. The increasing in number of the cases might be due to increased number of immigrants from the endemic area.

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To the Editor

Cryptococcemia in a Patient with Glioblastoma: Case Report and Literature Review

The incidence of primary malignant brain tumours has been on the rise, especially in the elderly population. In 2012, an estimated 22 910 new cases of primary brain neoplasms will be diagnosed in the United States. Roughly, 54% of these tumours are WHO Grade IV, Glioblastoma Multiforme (GBM). Known to have a dismal prognosis and high case mortality ratio, the median survival of this condition is generally less than one year from time of diagnosis and five-year survival is less than 5%.

For good performance status patients, National Comprehensive Cancer Network (NCCN) guidelines recommends treatment involving maximal safe resection followed by fractionated radiotherapy (RT) (usually to 60Gy) with concurrent daily temozolomide (TMZ); this should be followed by adjuvant TMZ for six months. In addition, many of these patients may require prolonged corticosteroid therapy to control the peri-tumoral and radiation-induced cerebral edema.

The incidence of opportunistic infections, particularly Pneumocystis Carinii Pneumonia (PCP), in HIV negative patients on TMZ appears to be higher[1]; this is likely attributable to TMZ induced lymphopenia. Due to the associated mortality and morbidity of PCP, recommendations have been made to place patients on prophylaxis during the concurrent temozolomide/RT phase of treatment. A recent literature review[2] reported the most frequently experienced infections were mucocutaneous candidiasis (28.2%), herpes zoster (12.8%), herpes simplex virus (10.2%), cytomegalovirus (CMV) (12.8%), PCP (7.6%), Hepatitis B virus (5.1%) and others (23%).

We present a case report of a patient with brainstem GBM treated with RT with TMZ who developed systemic cryptococcal infection.

Case report

The patient is a previously healthy 53-year-old Chinese businessman who presented with a sub acute frontal headache, slurring of speech and gait disturbances lasting a week. Initial magnetic resonance imaging (MRI) showed rim-enhancing lesions in the brainstem, which extended from midbrain to medulla (Figure 1). Biopsy was initially deferred in view of the precarious location and the patient was started on corticosteroids on the presumptive diagnosis of multiple sclerosis.

However, his symptoms progressed causing him to develop right hemiparesis. Repeat MRI revealed an interval increase in the size of the brainstem lesions. Stereotactic biopsy of the brainstem lesion was performed and histopathology confirmed GBM, WHO grade IV.

He was treated with definitive RT, and concurrent oral TMZ daily (75mg/m^2/day), up to brainstem tolerance (a total dose of 54 Gy in 27 fractions using intensity modulated radiation therapy). He received low dose oral dexamethasone 4 - 8 mg/day during radiotherapy. In addition, he was started on sulfamethoxazole and trimethoprim (Bactrim), for prophylaxis against PCP.

He planned to receive six cycles of adjuvant TMZ (5 days every four weeks, 150mg/m^2/day). After two cycles, interval MRI (three months post RT) showed increasing mass effect with midline shift and hydrocephalus. He was restarted on dexamethasone 4 mg/day and TMZ was continued for two further cycles.

However, the patient's mental state and Glasgow coma scale continued to fluctuate at six months post-RT. This was initially attributed to progressive brain tumor until the patient developed a persistent low-grade fever.

Full blood count showed normal hemoglobin, platelets and white cell count. Neutrophils were normal, however the absolute lymphocyte count was reported to be low (0.1 – 0.3 x 10^9/L).

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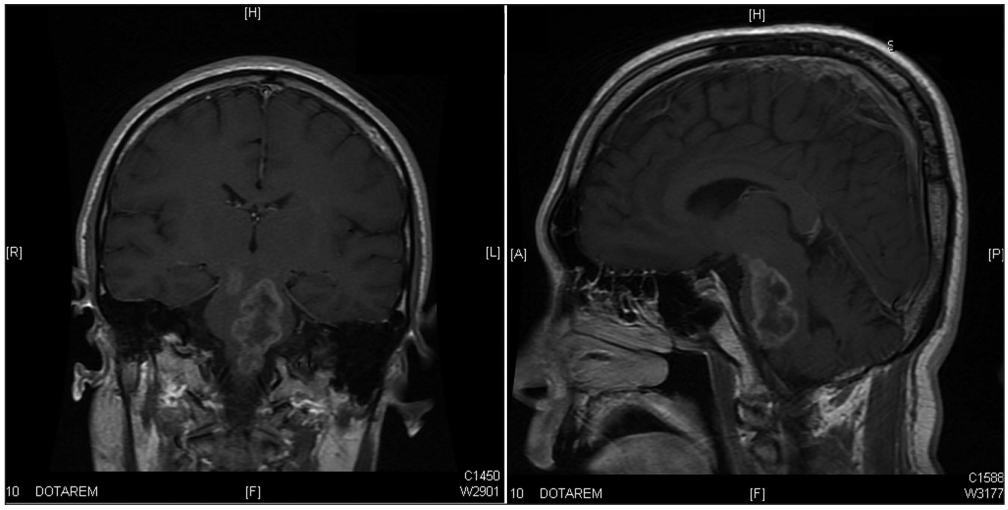

Figure 1: *Selected coronal and sagittal MR Brain (STEALTH) images on initial presentation.*

Inflammatory markers were deranged with C reactive protein being elevated at 180 mg/L and procalcitonin 4.7 ug/L.

Computed tomography (CT) of the thorax showed bilateral moderate pleural effusions with a moderate pericardial effusion and multiple enlarged mediastinal lymphadenopathy (Figure 2).

The CT of the brain once again showed enhancing lesions in the brainstem with perilesional edema.

Blood fungal cultures grew *Cryptococcus neoformans*, with confirmation on serum antigen testing.

Patient was started on intravenous (IV) amphotericin B and fluocytosine for two weeks for treatment of cryptococcemia. Repeat blood fungal cultures showed clearance of the organism, and laboratory markers improved. However, there was no improvement in his mental state. He was then placed on oral fluconazole therapy. Unfortunately the patient succumbed to his disease ten months from the initial diagnosis.

Discussion

Temozolomide plays an important role in the management of high grade gliomas (HGG).

A randomized, multicenter, Phase III EORTC trial (Stupp et al) demonstrated a significant overall survival benefit with the use of concurrent and adjuvant TMZ. Since then, it has become the standard of care for good performance status patients with HGG.

Temozolomide is an oral alkylating agent, which is a derivative of imidazotetrazine and a prodrug of dacarbazine. TMZ has an acceptable toxicity profile with the commonly encountered side effects being nausea (Grade 3 or 4 ~10%), vomiting (Grade 3 or 4 ~ 6%), headache, and fatigue. However, it is also known to cause severe and prolonged lymphopenia (Grade 3 or 4 ~ 55%) that may last for up to 12 months (NCCN). It has been proven quantitatively in a prospective study[3] conducted on patients receiving TMZ and RT where the CD4 nadir occurred approximately two months after initiating therapy, and about 40% of the patients had CD4 < 200 cells/mm^3. Interestingly, the CD4 counts remained suppressed throughout the following year, and subjects with CD4<200 had a survival detriment. In addition, the usage of prolonged corticosteroids to control peri-tumoural and radiation-induced

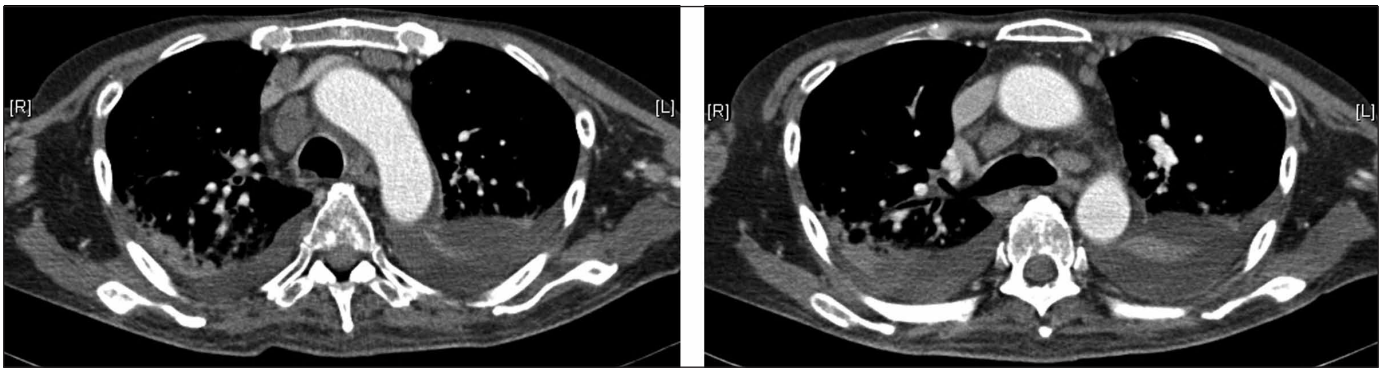

Figure 2: *Selected axial CT (contrast) images illustrating bilateral pleural effusion and enlarged mediastinal lymphadenopathy.*

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edema exacerbates the risk and severity of lymphopenia. Therefore, in view of the profound lymphopenia and higher incidence of PCP in patients with gliomas[1], Bactrim (sulfamethoxaole/trimethoprim 160mg) is recommended as prophylaxis in the concurrent phase. (NCCN)

Cryptococcal infection is an easily treatable condition, without which the sequalae may be severe. The key is in early recognition, identification and initiation of antimicrobial therapy. *Cryptococcus neoformans* causes an invasive fungal infection; it is prevalent in soil all around the world and also in areas frequented by birds – especially pigeons and chickens. Although prevalent, it rarely causes disseminated infection in healthy individuals. It tends to infect immunocompromised individuals: HIV positive patients with low CD4 counts, solid organ transplant recipients on immunosuppressive medications, patients with hematogenous malignancies and patients on long term glucocorticoids. Infection occurs via inhalation, and subsequently it disseminates hematogenously with a propensity to localize in the central nervous system. The clinical presentation tends to be variable; acute (days) or sub acute (weeks). Headache, lethargy, behavioral changes may develop over two to four weeks, and in roughly half the patients a febrile response is seen. Diagnosis of cryptococcal meningitis is clinched on examination of the CSF – with India ink stain, cryptococcal antigen testing and CSF culture. Systemic cryptococcal infection may be diagnosed on blood cultures or serum antigen testing (which has a sensitivity of 93-100% and specificity of 93-98%.) The treatment of cryptococcal infection consists mainly of antifungal agents and tapering ongoing immunosuppressive therapy. Antifungal treatment consists of induction therapy for two to four weeks, followed by consolidation therapy for eight weeks and finally maintenance therapy for 6 - 12 months. Induction therapy usually comprises IV amphotericin B (0.5 -1 mg/kg/day) and IV flucytosine (25mg/kg q 6 hourly), followed by consolidation and maintenance with oral fluconazole (6mg/kg/day).

The challenge, in this group of patients with gliomas and cryptococcal infection, is that both conditions may present in a similar manner. Fluctuating neurological symptoms and low-grade fever may be seen in either condition, however treatment for each is distinctly different. (Although uncommon, hypothalamic dysfunction from tumoural involvement may also produce low-grade fever.)

In our literature search, we have come across only one other case report[4] describing cryptococcal meningitis in patients with HGG. Extrapolating from studies done on primary prevention of cryptococcal infections in HIV patients,[5] it may be prudent to start patients with CD4<300 cell/uL on antifungal (fluconazole 400mg/day or itraconzole 200mg twice daily) prophylaxis ; in addition to Bactrim. Another, cost effective, alternative would be to monitor the CD 4 counts together with a weekly FBC and to start prophylaxis when the CD4 < 300.

In conclusion, we add to the growing body of evidence of opportunistic infections in this group of patients with HGG treated with RT, TMZ and corticosteroids; which is primarily due to lymphopenia and low CD4 counts.

Practitioners should have a high index of suspicion for opportunistic infections, over and above the ones mentioned earlier, in these patients and have a low threshold for investigating and starting appropriate anti-microbial therapy. The dose and duration of corticosteroids should also be reviewed regularly and tailed down to the lowest possible dose for symptom control.

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