**MORNING REPORT**

**The Kindergarten Cop’s Morning Report: Is Arnold Schwarzenegger Right? It Is Not a Tumor?**

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A 49-year-old male with untreated hypertension presents to an outside hospital with a constant throbbing headache in the bilateral occipital region associated with nausea and emesis and rated as 10/10 in pain severity for three weeks. He notes an unsteady gait for one day. A physical exam in the emergency department shows an ataxic gait, dysmetria, and intact strength. A head CT reveals a right cerebellar mass with evidence of mass effect. The patient is transferred to our facility for possible neurosurgical intervention; decadron is prescribed to reduce inflammation and mass effect.

The differential diagnosis of brain masses is extensive, but the approach to diagnosis should be timely to minimize delays in diagnosis. Inflammatory, infectious, and neoplastic processes would constitute leading etiologies. Due to its concerning prognosis, neoplastic disease must be excluded. In retrospective studies, an extended search for a primary neoplasm in the absence of an established history of cancer can lead to unnecessary imaging studies with delayed diagnosis. These studies are also unnecessary for most patients with primary brain tumors.

Approximately 15% of patients with brain metastases have neurologic symptoms related to these metastases as the presenting manifestation of their cancer. There is no significant difference in patient age or nature of presenting symptoms between patients with primary central nervous system (CNS) neoplasms and patients with metastatic brain disease, which further complicates the diagnostic approach. Multiple brain lesions are more likely in patients with brain metastases compared to patients with primary CNS lesions on imaging studies. MRI usually allows for better visualization of lesions, which may help differentiate malignant disease from non-neoplastic disease. Neoplasms that commonly metastasize to the brain include lung, melanoma, breast, colon, renal cell carcinoma, and cancer of unknown primary. Primary lung cancer represents about 50% of brain metastases in patients who do not have neurologic manifestations, but it is overrepresented in patients whose systemic malignancy presents as brain metastasis. The propensity of lung cancer to metastasize to the brain is due to its relative proximity to the systemic arterial circulation. With these facts, the next step would be to obtain an MRI. If clinical suspicion of brain metastases persists, a CT scan of the chest would be more sensitive than a chest X-ray as the next diagnostic step after brain MRI.

An MRI of the head reveals a dominant 2.5 x 2.1 x 1.8 cm heterogeneously enhancing mass in the right cerebellum and three subcentimeter cerebral enhancing lesions. The cerebellar lesion has significant regional mass effect, causing minimal ventricular dilatation without gross hydrocephalus. The radiologist feels this is likely metastatic disease, with infection less likely.

The differential still includes neoplastic diseases (primary or metastatic) and infectious conditions. Based on our knowledge of metastatic disease to the brain, it is important to ask the patient about pulmonary, gastrointestinal, and genitourinary complaints. Risk factors for cancer such as tobacco abuse and a family history of cancer will be important to assess, and a detailed skin exam looking for skin lesions consistent with melanoma will be required. Liver function tests (LFTs) may be helpful as hepatocellular damage can occur with liver metastases. In some cases, despite extensive investigations, the primary tumor remains unknown, which does not change survival; as such, lengthy work ups to find a primary should be avoided. Although the radiologist has favored a neoplastic etiology, systemic symptoms of infections should still be sought: a travel history, a list of sick contacts, and a detailed sexual history need to be completed since infectious conditions are still under consideration. The physical exam should also focus on signs of infections, and a CBC with a differential should be checked to evaluate for leukocytosis and a left shift.

The patient denies fevers, chills, sweating, or shortness of breath but does report a dry cough for two weeks. He denies anorexia but admits to weight loss, which he is unable to quantify. He denies abdominal pain, genitourinary symptoms, and skin lesions. He also denies sick contacts or significant travel history. There is no family history of cancer. He is a single heterosexual male with several simultaneous partners with whom he does not use protection. He denies a history of sexually transmitted diseases. He has a 30 pack-year history of tobacco use. He denies intravenous drug and alcohol abuse.

On physical exam, he has normal vital signs. Fundoscopic exam is normal. He has white plaques on the lateral aspects of his tongue and posterior pharynx, which scrape off leaving an erythematous base. Pul

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monary, cardiac, and abdominal examinations are normal. Neurologic examination reveals dysmetria and a mildly ataxic gait. The rest of the neurologic exam is normal. The skin exam shows no lesions. The patient’s electrolytes and renal function are within normal limits. His CBC shows leukopenia and lymphopenia. His LFTs shows normal transaminases with an elevated protein, low albumin, and elevated globulins.

The patient has a concerning sexual history, and his exam suggests the presence of oral candidiasis. An underlying diagnosis of HIV must be considered. Candidiasis tends to occur at a CD4 count less than 200 and suggests immunosuppression (placing the patient at risk for opportunistic infections). HIV infection is usually associated with a polyclonal hypergammaglobulinemia, which would explain his LFTs. His leukopenia and lymphopenia can be explained by a diagnosis of HIV. An HIV test and a CD4 count to assess the degree of immunosuppression should be checked.

Symptoms and signs of cerebral involvement occur in more than half of all patients with long-standing HIV. About 10% of patients have a neurologic disorder as the primary manifestation of HIV infection. Cerebral mass lesions are one of the prominent findings in this cohort who are highly susceptible to opportunistic infections as well as primary neoplastic processes.

The patient is found to be HIV positive, and his CD4 count is 31. SPEP testing indicates a polyclonal hypergammaglobulinemia.

The positive HIV test takes us in a new direction. The additional history, physical, and laboratory data defines our diagnostic search. The CD4 count is low enough for an HIV-associated opportunistic infection. The initial focus on metastatic disease to the brain was guided by the radiologist’s comments. It would now seem that the CNS lesions seen in this patient are more likely related to his HIV disease. A persistent search for a primary neoplasm while ignoring the patient's new data would lead to faulty treatment decisions.

The most frequent CNS lesions in HIV include primary CNS lymphoma and CNS toxoplasmosis. PML (progressive multifocal leukoencephalopathy), Kaposi sarcoma, cryptococcoma, and metastatic disease are much rarer. Usually lumbar puncture (LP) can be helpful when testing for either EBV virus (commonly associated with primary CNS lymphoma) through PCR testing or when testing for toxoplasmosis through serologies.

Testing for JC virus associated with PML can also be done on the LP fluid. However, since the patient had mass effect and edema, an LP would be contraindicated due to the risk of brain herniation.

Primary CNS lymphoma can improve with steroids, so it is crucial to decide whether to continue empirical steroids at this point. I would order serum toxoplasmosis serologies while remembering that CNS toxoplasmosis occurs due to reactivation rather than primary infection. Thus, IgG is more likely to be positive and helpful than IgM positivity. Serum PCR testing can be done but can be negative, as the disease is reactivating in the CNS. The multiple lesions seen in this patient are more likely to be seen in CNS toxoplasmosis than primary CNS lymphoma, so consideration should be given to start empirical toxoplasmosis treatment and stopping steroids.

If the patient has negative serological testing for toxoplasmosis, a stereotactic biopsy should be considered. Toxoplasma serum antibodies are tested. IgG is strongly positive at > 250 IU/mL; IgM is negative at < 0.9 IU/mL. Serum toxoplasmosis PCR is negative. The patient receives toxoplasmosis treatment with pyrimethamine, sulfadiazine, and folinic acid; decadron is stopped.

In reviewing the patient’s presentation, he reports having a headache, which is the most common symptom in CNS toxoplasmosis, and ataxia, the second most common focal deficit in toxoplasmosis. His CD4 count and positive serum IgG correlate with CNS toxoplasmosis. The number of lesions correlates with CNS toxoplasmosis rather than a primary CNS lymphoma.

The patient improves clinically, and a repeat MRI nine days after admission reveals remarkable improvement in the right cerebellar mass and resolution of the subcentimeter cerebral masses. He is discharged home but becomes lost to follow-up.

In medicine, it is important to reconsider your diagnostic approach as more information becomes available. An inability to do so can lead to bias. It is interesting to look at which processes we use in medical decision making, especially in the face of complex problems.

An important tool we use is the heuristic approach. Heuristic refers to experience-based techniques for problem solving, learning, and discovery. Heuristic methods are used to speed up the process of finding a satisfactory solution when an exhaustive search is impractical. Examples of this method include using a rule of thumb, an educated guess, an intuitive judgment, or common sense.

Anchoring and adjustment is a psychological heuristic that influences the way people intuitively as...
sess probabilities. People start with an implicitly suggested reference point (the “anchor”) and make incremental adjustments to it based on additional information to reach their estimate. Anchoring bias or focalism is a cognitive bias that describes the common human tendency to rely too heavily, or “anchor,” on one trait or piece of information when making decisions. In our case, continuing to anchor on the radiologist’s read of the MRI would have biased us and led us in the wrong diagnostic direction. The new anchoring heuristic was the patient’s HIV infection and its relation to his CNS lesions. In the end, Arnold was right: It was not a tumor.

Key Points
1. Lung cancer is the most common tumor that presents as CNS metastases; a cost-effective initial approach consists of a brain MRI and a CT of the chest.
2. The most common CNS lesions in HIV are CNS toxoplasmosis and primary CNS lymphoma; both are difficult to distinguish clinically. Treating empirically with repeat imaging is a reasonable approach in patients who do not have clear evidence of lymphoma.
3. Anchoring heuristic is an important tool in medical decision making, but care must be taken to avoid false anchoring, which can lead to bias.

References
1. Mavrakis AN. Diagnostic evaluation of patients with a brain mass as the presenting manifestation of cancer. Neurology 2005; 908-911