AJNR

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AJNR Am J Neuroradiol 2005, 26 (2) 205-206
http://www.ajnr.org/content/26/2/205

Imaging Neurotoxicity: Is a Picture Worth a Thousand Words?

The documentation and characterization of treatment-related neurotoxicity in primary CNS lymphoma (PCNSL) and other brain tumor patients have become increasingly relevant as therapeutic advances have improved long-term survival. The specific contribution of the disease itself and various treatment modalities to the development of neurologic and cognitive sequelae, however, remains to be elucidated. Whole-brain radiation therapy (WBRT) can produce leukoencephalopathy and may have a synergistic effect when combined with chemotherapeutic agents, particularly high-dose methotrexate (HDMTX). The neurotoxic potential of combined treatments is difficult to determine, especially when each technique can produce CNS damage individually. WBRT and HDMTX are considered the standard treatment for PCNSL. Although this treatment prolongs survival, there is a risk of neurotoxicity that increases with advanced age at treatment and in patients with prolonged disease-free survival. These regimens are primarily associated with the development of periventricular white matter damage through vascular injury, demyelination, and axonal necrosis. Several chemotherapeutic agents, particularly HDMTX and cytosine arabinose (ARA-C), have been shown to produce periventricular white matter abnormalities, but often less extensive than seen after combined technique treatment. The pathophysiological mechanisms of chemotherapeutic agents are not well understood, but several have been hypothesized, including demyelination, secondary inflammatory response, and microvascular injury. MTX-based chemotherapy, with or without osmotic blood-brain barrier disruption (BBBD), is efficacious and reduces the risk of delayed neurotoxicity and has been used more frequently in elderly PCNSL patients.

In this issue of the *AJNR,* Neuwelt et al report that in a group of PCNSL patients peritumoral enhancing abnormalities were associated with cognitive dysfunction at diagnosis, but not after a complete response to MTX-based chemotherapy and BBBD. Short- and long-term follow-up (available for a subset of patients) showed that some patients developed post-treatment diffuse or focal bilateral periventricular abnormalities, but they were not related to cognitive performance, which remained stable or improved over time (1). The authors concluded that "imaging changes, which are not tumor related, do not appear to be associated with cognitive decline." Several factors may, however, account for the lack of association between white matter abnormalities and cognitive performance. The treatment technique used may indeed produce only limited damage to the white matter, which falls below the threshold necessary to produce cognitive impairment. The authors reported cognitive function as a summary score, and no correlations between white matter abnormalities and specific cognitive functions (e.g., executive, processing speed) were reported. Therefore, it is unknown whether performance on some cognitive domains was associated with either diffuse periventricular or regional white matter abnormalities.

The association between diffuse treatment-related white matter abnormalities and the presence or severity of neuropsychological dysfunction in brain tumor patients is unclear. Treatment-induced cognitive dysfunction has been documented in several studies that included neuropsychological assessment; the cognitive domains found to be most sensitive to treatment side effects include attention and working memory, learning and retrieval of new information, and speed of information processing. A moderate association between treatment-related white matter changes and cognitive impairment was found in some, but not all, studies (2–5). Similarly, correlations between extent of white matter abnormalities and cognitive impairments have been reported in some studies of patients with disorders such as multiple sclerosis and HIV and in the elderly. The variable findings in the literature have been attributed in part to methodological factors (6), but it has also been suggested that more extensive white matter disease may be necessary to produce measurable cognitive deficits and that only specific cognitive domains, such as executive functions and information processing speed, are disrupted by diffuse white matter disease (6). The development and use of more advanced neuroimaging techniques may assist in clarifying some of these issues. For instance, recent studies assessing regional volumes of white matter in brain tumor survivors (7, 8) or using diffusion tensor imaging (9) have shown an association between white matter volume or integrity and cognitive dysfunction.

Neuroimaging and cognitive evaluations are best viewed as important complementary modalities in the assessment of treatment-related neurotoxicity and not surrogates for each other. There are instances in which some patients develop cognitive impairment in the context of relatively normal neuroimaging studies and others in which patients show only mild cognitive dysfunction but have extensive white matter disease. Further investigation of contributing variables, such as genetic risk factors or comorbid conditions that may place some patients at an increased risk for

developing either signs or symptoms of neurotoxicity is critical to improving our therapeutic approaches to brain tumor patients.

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Is There a Clinical Significance to the "Small Dark Tonsil"?

In the current issue of the *AJNR,* Jumper et al present the findings of a small T2-hypointense tonsil on the ipsilateral side of a metastatic level II cervical lymph node in two patients with an unknown primary tumor. Both patients underwent tonsillectomy, which revealed clinically occult squamous cell carcinomas in the "small, dark tonsil." We are left to ponder whether this appearance is a radiological curiosity or a significant finding that will substantially influence the workup of patients with unknown primary tumors. To fully understand the relevance of this new finding, I think it is important that we briefly review unknown primary tumors.

The definition of an unknown primary tumor has evolved over the past 20 years.

Most now accept the following description:

- A patient with one or more cervical masses that is pathologically proved to be a carcinoma;
- No history of previous malignancy or ablation of an indeterminate mass; and
- No evidence of a primary neoplasm based on specific symptoms, laboratory results, or findings on clinical examination, including those of panendoscopy.

In our practice, the most common diagnosis of an unknown primary tumor of the head and neck is squamous cell carcinoma; however, other subgroups such as adenocarcinoma, melanoma, and poorly differentiated malignant neoplasms are included under this heading. Between 3% and 5% of all head and neck cancers are of an unknown primary site. By using a thorough physical examination, operative endoscopy, and radiographic findings, physicians discover the "occult" primary site in 20–40% of cases. The initial workup begins with obtaining a thorough medical history and performing a complete head and neck examination augmented by radiographic imaging.

The imaging workup of an unknown primary is controversial. With the growth of multidetector technology, CT is the most commonly used technique to examine patients with head and neck cancer. The rapid image acquisition (<1 minute) and lower cost make CT a very attractive technique for initial examination of patients with an unknown primary site. Imaging findings that suggest a clinically occult site are asymmetrical fullness or an enhancing mass on the same side as the enlarged node in a subsite that is known to be a common location for clinically occult tumors. These subsites include the nasopharynx, tonsil, tongue base, and pyriform sinus. MR imaging has also been advocated because of its superior soft tissue characterization and multiplanar capabilities. Occult primary tumors may be suggested by asymmetrical tissue fullness, which is mildly hypointense to isointense on T1-weighted images and slightly isointense on T2-weighted images. Occult lesions typically enhance following administration of contrast medium. Positron emission tomography (PET) may also be beneficial for identifying the location of the clinically occult primary. The yield for locating the primary site with PET has been reported to be as high as 50%; however, the results are quite variable, and it is interesting to note that *both* patients with the tumor in the small dark tonsil had PET studies that showed no evidence of abnormal FDG uptake in the involved tonsil.

Following office evaluation and imaging studies, the patient with an unknown primary tumor is examined under anesthesia where direct laryngoscopy, esophagoscopy, and nasopharyngoscopy are performed. The ipsilateral tonsillar fossa and tongue base are identified as the primary site in 80% of such

cases (1). As a result, if no obvious site is identified, random biopsies are performed in the high-risk regions. Tonsillar biopsy tends to be insufficient in many cases of tonsillar cancer, so ipsilateral tonsillectomy is suggested. One study found a 35% increase in the ability to detect occult primary by using ipsilateral tonsillectomy (2). Some authors recommend bilateral tonsillectomy owing to a 10% incidence of bilateral occult squamous cell carcinoma in the tonsillar fossa, but this is a controversial issue and not considered the standard of care (3). The identification of an occult primary tumor site is of critical importance in determining the patient's treatment. Without an identified primary tumor site, standard therapy consists of radiation therapy to all mucosal surfaces of the head and neck, as well as both cervical lymphatic basins. Either pre- or postradiation neck dissection is also performed for N_2 or greater neck disease, which can result in significant morbidity related to xerostoma and associated swallowing difficulties. On the other hand, if an occult primary tumor can be identified, the radiation can be directed to the primary site alone and significant morbidity can be avoided.

With this background, we now must determine what the potential impact of the "small dark tonsil" reported in this manuscript may be. First, we must congratulate Jumper et al for their excellent observation. I think the findings are subtle, but they are real. It is intriguing that the signal intensity characteristics could not be explained by the pathologic results. One would expect a tumor that exhibits such T2 hypointensity to exhibit substantial desmoplasia or fibrosis. These findings were not, however, present. The next question is what is the incidence of this finding in the normal population? It would be helpful to retrospectively and prospectively review the presence of a "small, dark tonsil" in a normal population to determine its true incidence. It would also be helpful to retrospectively and prospectively evaluate the MR imaging studies obtained in patients with an unknown primary tumor site to determine whether similar findings can be observed. To do this, one would have to make sure that the patients have never undergone a prior tonsillectomy or random biopsies of the tonsil, because the postsurgical changes may result in hemorrhage or fibrosis, which could result in findings similar to those Jumper et al describe.

Without a thorough understanding of the diagnostic accuracy of the small, dark tonsil, we feel that the real clinical impact of this imaging finding is to underscore the importance of performing ipsilateral tonsillectomy in patients with unknown primary tumors with isolated metastases to level II or III. The otolaryngology surgeons and radiation oncologists have a high suspicion of an ipsilateral tonsillar carcinoma when patients present with isolated unilateral level II and III nodal metastases. This is based on the lymphatic drainage previously described by Rouvierre (4). It is not clear whether Jumper et al have identified subtle changes of early tonsillar carcinoma; however, their subtle findings did correspond with the presence of a clinically occult tumor. Both of these tumors would not have been detected with CT, because the tonsil was not enlarged and CT lacks the ability to identify such subtle soft tissue alterations. One can easily imagine a scenario in which the CT findings were negative and the patient would have been treated for an unknown primary tumor if the treating clinician did not choose to perform a tonsillectomy. Although Jumper et al never claim this, it is apparent that MR imaging is the preferred cross-sectional technique at their institution for initially examining patients with unknown primary tumors. These subtle findings suggest that MR imaging may have some advantages over CT. Until these findings are fully investigated, I think it is premature to say that one cross-sectional technique is clearly superior to another for evaluating an unknown primary tumor.

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