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INTRODUCTION

- There are no standardized criteria for the objective evaluation of suspected case reports of progressive multifocal leukoencephalopathy (PML).
- The primary goal of PML classification criteria was to apply a hierarchy of evidence to objectively classify cases as confirmed, high- or low-suspect, indeterminant, or ruled out based on all available clinical data using Brighton Collaboration methodology.¹ Case reports that could be neither confirmed nor ruled out were assessed as high- or low-suspect or insufficient information. With additional follow-up information, the case would be reassessed and classified according to all available information.
- On the basis of experience and challenges associated with evaluating PML case reports (Table 1), Biogen Idec and Elan Pharmaceuticals have developed this classification system for objectively assessing PML case reports in natalizumab-treated patients.
 - Biogen Idec and Elan Pharmaceuticals have years of experience in evaluating suspected PML case reports.
 - This knowledge is the basis for extensive education about PML provided to prescribers of natalizumab.
 - Prescribers have a high level of clinical vigilance and intensively screen patients for PML.

TABLE 1. Challenges of Evaluating PML Case Reports in Natalizumab-Treated Patients

• Some cases need repeat MRI and CSF testing over weeks or months to be fully evaluated (eg, MRI may be consistent with PML but CSF tests negative)
• Use of various types of JCV DNA PCR assays used globally with variable sensitivity and specificity (qualitative or quantitative, ultrasensitive or not)
• In a few cases, despite extensive due diligence, there is insufficient clinical information to allow case classification
• Differentiation between PML and MS relapse can be challenging
• Early detection of PML cases is increasing, but presymptomatic detection makes it difficult to utilize the diagnostic requirements of a symptomatic progressive neurological diagnosis
CSF=cerebrospinal fluid; JCV=JC virus; MRI=magnetic resonance imaging; MS=multiple sclerosis.

OBJECTIVE

- To propose a PML classification system using different levels of diagnostic certainty and a hierarchy of clinical evidence.

METHODS

- Brighton Collaboration methodology was used, which has been successfully applied to the classification of adverse events with vaccines.^{1–5}
- To evaluate the new PML classification system, an impact analysis was conducted on all global confirmed, suspected, and ruled-out PML cases as of July 5, 2011. All confirmed, suspected, and ruled-out cases have been re-reviewed based on the new criteria.
 - Predictive values (positive and negative) were calculated based on re-evaluation of suspected PML cases at 3 different time points (October 2010, January 2011, and April 2011).
 - The positive predictive value is the proportion of high-suspect cases that become confirmed cases.
 - The negative predictive value is the proportion of low-suspect cases that become ruled-out cases.
 - Values for each time point were reported as a range of predictive values.

RESULTS

- The new classification system addresses some of the limitations of the original classification system (Table 2) and provides standardized criteria using objective data for 5 different levels of case definitions based on diagnostic certainty (Table 3).

TABLE 2. Characteristics of Original Versus New PML Case Classification Criteria for Natalizumab-Treated Patients

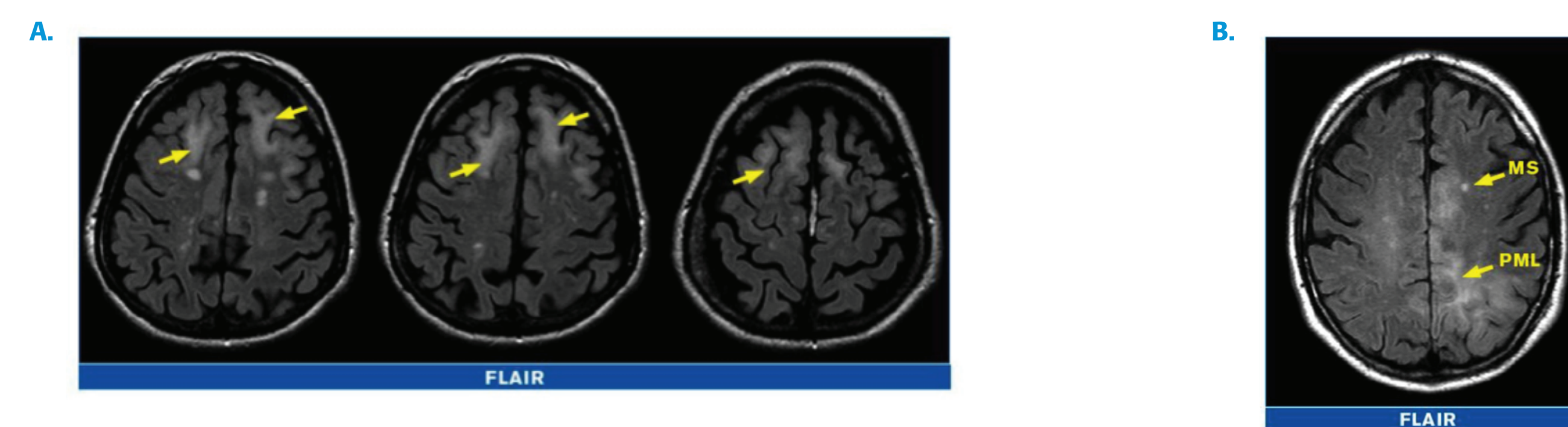
Original	New
1. Binary classification (confirmed or ruled out)	1. Classification stratified on diagnostic certainty levels (level 1 to level 5; described below)
2. Case remains in suspected PML category until able to confirm or rule out	2. Immediate classification based on available data
3. No category with insufficient information	3. Category with insufficient information
4. Ultrasensitive, quantitative PCR assay for JCV DNA required to confirm a case of PML	4. Any type assay for JCV DNA acceptable (qualitative or quantitative, ultrasensitive or not)

TABLE 3. New PML Classification System with 5 Levels: Definitions and Examples

Level	Definition	Examples
Level 1 – Confirmed Case*	<ul style="list-style-type: none"> • Brain biopsy or brain from postmortem examination showing evidence of viral cytopathic changes on H&E stain associated with either positive immunohistochemistry for SV40 or in situ hybridization for JCV DNA OR • CSF with evidence of JCV DNA, preferably by ultrasensitive quantitative PCR testing (limit of quantification of ≤ 50 copies/mL), or JCV DNA on brain biopsy by PCR, AND <ul style="list-style-type: none"> – Detailed brain MRI findings* consistent with PML AND PREFERABLY – New or progressive clinical symptoms suggestive of PML 	<ul style="list-style-type: none"> • A patient with a brain MRI reported to be “suspicious” for PML, with no further details provided, underwent 2 lumbar punctures that both tested negative for JCV DNA in CSF at a local laboratory. The patient underwent a brain biopsy that was found to be consistent with PML based on histopathology findings (immunohistochemistry and/or in situ hybridization) • A patient with a brain MRI showing hyperintense, subcortical lesions on T2/FLAIR consistent with PML and had CSF that tested positive for JCV DNA at a local laboratory (qualitative assay)
Level 2 – High-Suspect Case*	<ul style="list-style-type: none"> • CSF with positive JCV DNA by PCR (using any PCR assay) OR • Detailed brain MRI findings* consistent with PML (eg, hyperintense lesion in T2/FLAIR, subcortical lesions, diffuse lesions, lesions atypical of MS, including new lesion with or without gadolinium enhancement) (Figure 1) 	<ul style="list-style-type: none"> • A patient with CSF that tested positive for JCV DNA and had no MRI report • A patient with a detailed MRI report with subcortical lesion and hyperintense lesion in T2/FLAIR; CSF tested negative for JCV DNA
Level 3 – Low-Suspect Case*	<ul style="list-style-type: none"> • Brain MRI reported as “suspicious” for PML without further description OR • New or progressive clinical symptoms suggestive of PML (eg, recent changes in behavior or personality, hemiparesis, language disturbances, retrochiasmatal visual deficits, or new onset of seizures developing within weeks) 	<ul style="list-style-type: none"> • A patient with a brain MRI “suspicious” for PML, with no further details provided, and had CSF that tested negative for JCV DNA at a local laboratory • A patient developed new cognitive and personality changes suggestive of PML, but had not yet undergone MRI or CSF testing
Level 4 – Insufficient Information*	<ul style="list-style-type: none"> • Insufficient information is available to either confirm or rule out a diagnosis of PML 	<ul style="list-style-type: none"> • A neurologist reported that another neurologist who wished to remain anonymous was currently evaluating a patient who had been treated with natalizumab and was now suspected of having PML. No further details were provided, including MRI results or CSF testing. The treating neurologist wished to remain anonymous so no additional follow-up queries could be generated. Therefore, despite due diligence, no further information was available for the case
Level 5 – Ruled-Out Case*	<ul style="list-style-type: none"> • Brain biopsy specimen or postmortem brain examination does not show any evidence of JCV infection based on immunohistochemistry or in situ hybridization analysis OR • Alternative diagnosis is present OR • The presence of 2 of 3 of the following criteria: <ul style="list-style-type: none"> – CSF negative for JCV DNA – MRI is not consistent with PML – Clinical improvement is present, or absence of clinical progression 	<ul style="list-style-type: none"> • A patient with a brain MRI “suspicious” for PML, with no further details provided, had CSF that tested negative for JCV DNA at a local laboratory. The patient then underwent a brain biopsy that showed no evidence of JCV by immunohistochemistry or in situ hybridization • A patient experienced seizures that were suspicious for PML and had an MRI that showed “ring enhancing lesions”; CSF tested negative for JCV DNA at FOCUS Diagnostics laboratory (ultrasensitive PCR). The treating physician ruled out PML by providing an alternative diagnosis of MS exacerbation characterized by seizures • A patient developed new onset of hemiparesis and was suspected of having PML. A brain MRI showed multiple lesions typical of MS. The patient was treated with corticosteroids and clinically improved

*Once classified as level 1 (Confirmed), a case would remain as level 1.
 *Level 2 and 3 cases (High-Suspect or Low-Suspect, respectively) are more dynamic. For example, a level 2 case may become a level 1 (Confirmed) case following receipt of new information, or a level 3 case may become a level 5 (Ruled Out) case with further follow-up.
 *Level 4 (Insufficient Information) will be utilized only after exhaustive due diligence has failed to provide sufficient information to classify a case.
 *Level 5 (Ruled Out) cases are likely to remain in this category (unless new information impacting classification is received). PML case reports will be considered Ruled Out if follow-up on an initial report of suspect PML reveals that the physician’s suspicion has resolved due to patient’s clinical improvement, MRI negative for PML, or CSF negative for JCV DNA and no further workup is planned.
 *Detailed MRI findings include hyperintense lesions in T2/FLAIR, subcortical lesions, diffuse lesions, lesions atypical of MS, including a new lesion with or without gadolinium enhancement.
 FLAIR=fluid-attenuated inversion recovery; H&E=hematoxylin and eosin; PCR=polymerase chain reaction.

FIGURE 1. Detailed MRI FLAIR Images Showing (A) Bilateral Subcortical PML Lesions in Frontal Lobes and (B) Differences in Lesion Borders with MS Lesions Well Circumscribed and PML Lesions Ill-Defined



Impact Analysis

- At the time of this analysis (July 2011), there were 145 confirmed cases of PML in natalizumab-treated patients using the original case classification system.
- The impact analysis indicated that all existing confirmed and ruled-out PML cases using the original classification system align with the new classification system.
 - Two cases (from previous suspect category) were assessed with the new criteria as level 4 (insufficient information) cases due to insufficient information despite intensive diligence and multiple attempts to obtain follow-up information.
 - As of July 2011, all 145 confirmed PML cases using the original classification system were classified as level 1 (confirmed) using the new system.

- The new PML classification system demonstrated a favorable positive predictive value (PPV equal to 59%–85%) for high-suspect cases and a favorable negative predictive value (NPV equal to 90%–95%) for low-suspect cases.

CONCLUSIONS

- Using Brighton Collaboration methodology and expert input, Biogen Idec and Elan Pharmaceuticals have developed a PML classification system that:
 - Provides a tiered approach to PML case classification (levels 1 to 5) based on an objective hierarchy of clinical evidence;
 - Allows real-time reassessment of cases based on currently available data;
 - Accommodates various JCV DNA assays (eg, qualitative or quantitative, ultrasensitive or not) that are available in different global geographic locations;
 - Considers unique challenges in natalizumab-treated patients, such as intensive screening and early detection (ie, suspected case report of PML still under diagnostic evaluation), and the often-challenging differentiation between PML and MS.
- The clinical utility of the classification criteria has been tested for 145 confirmed PML case reports as of July 2011 with the input of PML experts.
 - Based on the new PML classification system, the number of confirmed PML cases remains unchanged, and there is no impact on the overall benefit-risk profile of natalizumab.
- The objective nature of the classification criteria has aided more timely review of case reports as well as aided in more focused case follow-up information requests.
- Although criteria have demonstrated utility for the evaluation of suspected case reports of PML associated with natalizumab, this classification may have more broad utility in evaluating case reports of PML associated with the use of other therapies.

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Disclosures

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