

venous part of the story. Unimaged arterial air may have led to a small but strategic lacunar lesion (e.g., in the internal capsule) that was not visualized on diffusion-weighted MRI.

Author Response: Andrew J. Westwood, Thanh N. Nguyen, Boston: Coebergh et al. agree that the most plausible mechanism for air in the cavernous sinus is a retrograde venous embolism. In reviewing our article, we concur that the discussion may be misleading; we used the term TIA to denote a clinical syndrome which resolved within 1 hour rather than to referring to a proposed mechanism.

We know that the patient was sitting upright at the time. Because air is less dense than blood, it is possible that the embolism traveled retrogradely to produce the transient symptoms. On review of the catheter placement seen on chest x-ray at time of admission, the line appears to be placed with the tip in the superior vena cava. We refer to a study² that monitored paradoxical emboli in patients with transatrial shunts after central line placements. The head CT shows presence of air in the sinus and makes it more likely that it was retrograde. However, paradoxical air embolism should always be considered in patients with transatrial shunts. We thank Coebergh et al. for raising this important issue.

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ACUTE MYELOID LEUKEMIA IN ITALIAN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH MITOXANTRONE

Anke Stroet, Ralf Gold, Andrew Chan, Bochum, Germany: Martinelli et al.¹ reported a relatively large incidence of therapy-related acute myeloid leukemia (TRAL) in a retrospective Italian MS cohort (0.93%). In contrast, we observed a much lower TRAL incidence in a large retrospective German cohort (range of 0.25% to 0.41%)² similar to 2 prospective studies,^{3,4} despite observation intervals comparable to Martinelli et al. In addition to methodologic aspects, differences may also relate to other factors including pretreatment and treatment protocols.

A 3-month treatment regimen is common in Germany, as demonstrated in one pivotal phase III

trial⁵; 68.9% of the Italian patients were treated bimonthly or monthly. In addition, dose adjustment—according to leukocyte nadir—is not described in the Italian study but is required per the Summary of Product Characteristics in Germany. It is conceivable that higher dosages over a shorter time may pose an increased risk for toxicity. Potentially additive or genotoxic cotreatment further complicates data analysis. Besides the introduction of uniform treatment algorithms, larger collaborative studies should focus on potential risk factors as well as individual predisposition, e.g., pharmacogenomic characteristics.

This is important since treatment alternatives are still sparse in rapidly progressing secondary progressive MS.

Author Response: Vittorio Martinelli, Laura Straffi, Giancarlo Comi, Milan, Italy: We agree that there is variability in TRAL incidence in patients with MS. We observed this in our multicenter study¹ where TRAL incidence among centers ranged from 0/167 to 4/115. It is also recognized that published single cohort studies may be more biased toward high incidence than unpublished data.

Our data contradict other studies^{2–4} with similar observational follow-up, but there were methodologic differences, including sample size (3,220¹ vs 1,156² or 802³); follow-up of at least 1 year; and the closely linked network of Italian centers. Furthermore, 2 new acute myeloid leukemia cases were confirmed in the last year in our original cohort.

As Chan et al. suggest, we suspect that risk might be related to a specific treatment regimen or cotreatment, but we did not find this association. Moreover, monthly³ and 3-monthly infusions² appear to have similar incidences. We believe that without a means of identifying susceptibility,⁶ the risk of TRAL must always be considered, perhaps with some type of “regional” stratification. There are currently 106 cases reported worldwide, one-third of which may be fatal.

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