Radiolabeled Leucocyte Imaging in Diffuse Granulomatous Involvement of the Meninges in Wegener’s Granulomatosis: Scintigraphic Findings and Their Role in Monitoring Treatment Response to Specific Immunotherapy (Humanized Monoclonal Antilymphocyte Antibodies)

Joseph M. Murphy, Kottekkattu K. Balan, Andoni Toms, Beatriz Gomez-Anson, and Martin Lockwood

BACKGROUND AND PURPOSE: Diffuse involvement of the meninges by remote granulomas in Wegener’s granulomatosis is rare. This study reports the radiolabeled leucocyte imaging findings in five such patients. The diagnosis was made by MR imaging in five patients and confirmed in four by findings at meningeal biopsy. The potential role of serial radiolabeled leucocyte examinations in assessing treatment response is discussed.

METHODS: Three of the five patients underwent whole-body planar 111In-labeled leucocyte imaging. Two of these patients had serial imaging and one had, in addition, a 99mTc-HMPAO-labeled leucocyte single-photon emission CT brain examination. Two of the five patients had whole-body planar 99mTc-HMPAO-labeled leucocyte imaging. Of these, one patient had serial imaging. The radiolabeled leucocyte imaging findings were correlated with MR findings and with the patients’ clinical course.

RESULTS: In four patients there was a midline linear area of increased tracer uptake in the brain, and in one of these, tracer uptake also extended laterally over the brain convexity. In two patients linear tracer uptake extended in an inferolateral direction from the midline. These abnormalities correlated with meningeal thickening in the falx, over the brain convexity, and in the tentorium cerebelli on MR images. Serial imaging in three patients revealed a reduction or disappearance in tracer uptake after treatment with anti-CD52, which correlated with clinical improvement.

CONCLUSION: In patients with Wegener’s granulomatosis, abnormal uptake corresponding to meningeal thickening can be seen on planar radiolabeled leucocyte images. Leucocyte imaging may be useful for monitoring treatment response.

Our institution is a national and international referral center for patients with Wegener’s granulomatosis (WG). Whole-body planar leucocyte imaging is commonly performed for the initial assessment of disease activity and for monitoring treatment response in various sites, including the nose, paranasal sinuses, gastrointestinal tract, and lungs. While imaging these patients we have become aware of a characteristic and hitherto unreported pattern of tracer uptake in the brain of patients with diffuse meningeal disease associated with WG. To our knowledge, these findings have not previously been reported. We describe the scintigraphic findings in this group of patients, correlate these with the MR imaging findings, and discuss the potential role of white blood cell imaging in assessing intracranial response to treatment.

Methods

The radiolabeled leucocyte imaging studies of five patients with diffuse WG of the meninges (demonstrated by MR imaging in all cases and proved by biopsy findings in four patients) were reviewed. The five patients comprised three wom-
en and two men with a mean age of 55 years (range, 43–67 years). Cerebral involvement was suspected in all patients because of severe persistent headaches.

Of the five patients, three underwent whole-body planar $^{111}$In-labeled leucocyte imaging. Two of these patients had serial imaging and one had, in addition, a $^{99m}$Tc-HMPAO-labeled leucocyte single-photon emission CT (SPECT) brain examination. Two of the five patients had whole-body planar $^{99m}$Tc-HMPAO-labeled leucocyte imaging. Of these, one patient had serial imaging.

For both the $^{111}$In-labeled and $^{99m}$Tc-HMPAO-labeled leucocyte whole-body examinations, in vitro labeling was performed by initial collection of 50 mL of blood into a syringe containing 6 mL of acid citrate dextrose. Leucocytes were then separated by differential centrifugation. The cells were maintained in plasma throughout the separation and labeling process to minimize leucocyte activation (1). The leucocytes were then labeled with 16 MBq $^{111}$In-tropolonate or 400 MBq of $^{99m}$Tc-HMPAO using standard techniques (1, 2). Anterior and posterior whole-body images were obtained 3 and 24 hours after intravenous injection of the isotope-labeled leucocytes. The MR examinations were performed on a 0.5-T Signa Horizon General Electric MR unit, a 1.5-T Signa Horizon General Electric MR unit, or a 1.5-T LX General Electric MR unit. Axial fast spin-echo (FSE) proton density–weighted sequences with parameters of 3000/15/1 (TR/TE/excitation), field of view = 22 × 22, section thickness = 6 mm with a 1-mm gap, and matrix = 256 × 256, and FSE T2-weighted sequences with parameters of 3000/105/1, field of view = 22 × 22, section thickness = 6 mm with a 1-mm gap, and matrix = 256 × 256 were acquired in all patients. All patients also had SE T1-weighted imaging (500–5409/14/2, field of view = 20–22 × 20–22, section thickness = 5 mm, matrix = 256 × 256) before and after intravenous administration of 0.1 mL/kg gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany). Images were obtained in either axial or coronal planes, with or without fat suppression. The examinations were transferred to a workstation and reviewed independently by two consultant neuroradiologists; a consensus opinion was obtained when necessary. The radiolabeled leucocyte imaging findings were correlated with MR findings and with the patients’ clinical course.

Results

Vertical linear midline uptake of radioisotope was seen in the brain in four of the five patients (Figs 1A and 2A). All four patients had anterior and posterior whole-body planar scintigraphy with $^{111}$In as the tracer in two and $^{99m}$Tc-HMPAO as the tracer in the other two. The extent of tracer uptake varied from a small focus in one patient to widespread midline activity in the remaining three patients. In both patients imaged with $^{99m}$Tc-HMPAO, tracer uptake was more marked on the 3-hour images than on the 24-hour images. In one of the patients imaged with $^{111}$In, the 3-hour images were not available for analysis. Abnormal midline tracer activity was seen on the posterior images in all patients but on the anterior views in only one patient. When correlated with MR images, obtained at a mean of 61 days from the radiolabeled leucocyte study (range, 12–134 days), the midline linear tracer uptake corresponded to thickening of the meninges of the falx in all four patients (Figs 1A and B, and 2A and B).

In two patients, linear tracer activity was seen extending in an inferolateral or lateral direction from the midline to the periphery (Figs 2A and 3A). In one patient, this was bilateral and extended from the caudal aspect of the associated linear midline activity when imaged with $^{99m}$Tc-HMPAO-labeled leucocytes (Fig 2A). The increased uptake was only appreciated on the posterior images and was most pronounced at 3 hours. This correlated with bilateral thickening of the tentorium cerebelli on MR images obtained 43 days previously (Fig 2B). In the other patient, abnormal right-sided linear uptake was the only abnormality on a $^{111}$In-
labeled leucocyte scintigram (Fig 3A). The tracer uptake was seen on both anterior and posterior planar views and was most marked on the 24-hour images. There was thickening and enhancement of the right tentorium cerebelli on an MR examination performed 17 days after the leucocyte scan (Fig 3D). A $^{99m}$Tc-HMPAO-labeled leucocyte SPECT study was also performed in this patient, and this also clearly demonstrated increased uptake in the right tentorium cerebelli (Fig 3B and 3C).

In one patient, a $^{99m}$Tc-HMPAO-labeled leucocyte examination revealed a curvilinear area of tracer uptake that extended laterally from a midline point deep to the calvaria (Fig 2A). This was best seen on the posterior view obtained at 24 hours. This area correlated with thickening of the dura overlying the brain convexity on MR images (Fig 2B). Radiolabeled leucocyte imaging underestimated the extent of involvement of the dura overlying the cortex as compared with MR imaging. Three of the other four patients had dural thickening and enhancement overlying the cortex on the MR images that was not evident on the leucocyte images (Fig 1A and B).

Three patients underwent serial radiolabeled leucocyte imaging. The leucocyte studies were labeled with indium-111 in two patients and with $^{99m}$Tc-HMPAO in one patient. All patients were treated with anti-CD52 and clinically responded to treatment with resolution of severe debilitating headaches. One patient with tracer uptake consistent with inflammation of the right tentorium cerebelli showed no abnormal uptake after treatment (Fig 3A and E). Subjective evaluation of the images in the other two patients revealed a significant reduction in midline tracer activity after treatment (Figs 1A and C and 2A and C). One of these patients also showed a complete absence of tracer uptake, which had previously correlated with inflammation of the meninges of the tentorium cerebelli and brain convexity after treatment (Figs 1A and C, and 2A and C). MR images in all three patients showed reduced but persistent dural thickening and enhancement. A summary of the radiolabeled leucocyte and MR imaging findings in all five patients appears in the Table 1.

Discussion

WG is a multisystem disorder characterized pathologically by necrotizing granulomata that commonly occur in the upper and lower respiratory tract, systemic arterial and venous vasculitis, and focal necrotizing glomerulonephritis (3–9). The onset of the disease usually occurs between 40 and 50 years of age, and 90% of patients have been reported to present with upper or lower respiratory tract symptoms (3, 7). Myalgia, arthralgia, deafness, painful proptosis, diplopia, and hematuria are other recognized presenting signs and symptoms.

Nervous system involvement in WG occurs in 22% to 54% of patients, and usually manifests as a peripheral neuropathy or a mononeuritis multiplex (4, 6–8). Involvement of the CNS occurs in only 2% to 8% of patients (3, 6, 8). Drachman (7) has identified three processes by which the nervous system may be affected in WG. In a review of 104 patients, vasculitis was the most common mechanism of nervous system involvement, affecting 28% of patients and resulting in cerebral hemorrhage, thrombosis, or a peripheral neuritis. In 26% of patients, there was encroachment upon the brain, meninges, or peripheral nerves from orbital, nasal,
or paranasal disease. Remote isolated granulomatous lesions affecting the brain, meninges, parietal bone, and cranial nerves occurred in only 4% of patients (7). Subsequent series have confirmed these three disease mechanisms but have documented a lower prevalence of nervous system involvement since the advent of effective therapy (3, 4, 6, 8).

Diffuse meningeal involvement by remote granuloma remains an uncommon manifestation of WG. Drachman (7) documented meningeal infiltration by a necrotic and granulomatous process in only one of 104 patients. Meningeal involvement was not seen in the 85 patients reported by Fauci et al (6), and was present in only one of 324 patients, causing multiple cranial neuropathies and severe headaches, in the series reported by Nishino et al (8). The CT and MR appearances have been well documented (10–15). Diffuse symmetrical linear thickening and enhancement of the dura are usually seen, although focal and nodular thickening has also been reported. There may be associated large areas of high signal in the white matter on T2-weighted MR images. The leptomeninges are usually not involved (12, 13). Results of dural biopsy in such cases have revealed necrotizing granulomata, multinucleated giant cells, and lymphocytic infiltration (10, 11–13). Thickening and fibrosis of the pia-arachnoid with granulomata surrounding blood vessels have also been reported (12). Results of a meningeal biopsy were consistent with WG in four patients from our series. In addition to the necrotizing granulomata characteristic of WG, there was usually an infiltrate of chronic inflammatory cells, such as B and T lymphocytes, eosinophils, histiocytes, plasma cells, and macrophages. It is therefore not unexpected that ra-
Radioisotope-labeled leucocyte examinations have been shown to be useful, noninvasive investigations in both the diagnosis and monitoring of disease activity in WG and other systemic vasculitides (15). A significant advantage of these techniques is the ability to acquire whole-body images. Nasal uptake of radiolabeled leucocytes may help differentiate WG from microscopic polyangiitis (16). Leucocyte imaging allows an assessment of the extent of deep tissue involvement and the progression of disease activity, which is often difficult to assess clinically. Scintigraphy has indeed been shown to be superior to conventional radiography or CT for detecting and monitoring vasculitic involvement of the respiratory tract (16). It is also useful for detecting unsuspected sites of disease activity, facilitating earlier institution of specific therapy.

Headache is a particularly difficult symptom to deal with in patients with WG. The predilection of the disease for sites close to the intracranial air spaces frequently leads to concern that hitherto unsuspected intracranial disease may be responsible. Lesions may be difficult to localize, and similar symptoms may be caused by granulomatous vasculitis presenting as posterior uveitis, otitis media, retroorbital pseudotumor, sinusitis, and the meningeal involvement detailed above. The ability to image the development of intracranial inflammation by scintigraphy can be extremely useful in clarifying these differential diagnoses, which, taken individually, are otherwise difficult to elucidate once the possibility of infection has been eliminated.

Marienhagen et al (17) reported the use of $^{99m}$Tc-HMPAO cerebral SPECT perfusion examinations in the diagnosis of cerebral vasculitis in patients with WG. They documented regional cerebral blood flow abnormalities not matched by abnormalities on anatomic MR images and suggested $^{99m}$Tc-HMPAO SPECT perfusion imaging may be sensitive for the detection of early cerebral vasculitis in WG before irreversible structural brain damage or gross clinical symptoms appear. To our knowledge, the scintigraphic appearance of meningeal involvement by WG has not previously been reported. Reuter et al (16), in a previous report from our institution, mentioned but did not describe meningeal uptake in one patient with WG. In the evaluation of patients with WG, focal or linear uptake in the region of the brain convexity, falx, or tentorium cerebelli on planar radiolabeled leucocyte images suggests the presence of meningeal involvement. This warrants further assessment by MR imaging, because leucocyte imaging tends to underestimate the extent of involvement.

Diffuse meningeal thickening may occur in other conditions (18–24). Primary or secondary dural tumors, such as meningiomas, lymphomas, fibromas, and metastases, should not be positive on leucocyte images. Infectious meningitis (including tuberculosis) and late-stage syphilis can usually be distinguished from WG clinically. Hypertrophic cranial pachymeningitis is a rare condition, characterized by thickening and fibrosis of the dura with infiltration by chronic inflammatory cells; but this condition can again usually be distinguished on clinical grounds (24). Although at MR imaging leptomeningeal thickening and enhancement constitute the most common pattern of meningeal involvement in neurosarcoidosis, dural thickening and enhancement indistinguishable from that seen in WG can occur (18, 20).
In three patients in this series treated with anti-CD52, subjective evaluation of serial leucocyte images revealed reduced or absent intracerebral tracer uptake. These findings correlated with clinical improvement. MR images in all three patients showed reduced but persistent dural thickening and enhancement. Serial MR and CT studies have been used to monitor treatment response in patients with diffuse meningeal involvement by WG treated by immunosuppression (12, 13, 14). A return of MR imaging findings to normal or a reduction in the degree of dural thickening and enhancement after treatment has been shown to correlate with clinical improvement. Residual persistent dural thickening has, however, occasionally been reported after treatment, as was seen in our patients (12, 13). It is then not clear whether this represents active disease or residual fibrosis. Radiolabeled leucocyte imaging has been shown to be useful in monitoring disease progression and response to treatment at other sites, particularly the respiratory tract and nasal cavity (16). Radiolabeled leucocyte imaging reflects abnormal migration and localization of white cells and therefore may be a useful adjunct in cases with residual meningeal thickening on MR images after treatment to determine whether this represents active disease.

**Conclusion**

Radiolabeled leucocyte imaging is a valuable technique in the assessment and monitoring of patients with systemic vasculitis and is commonly performed in patients with WG to evaluate disease activity in the nasal cavity, lungs, and gastrointestinal tract. Although meningeal involvement by WG is rare, it can be identified on planar leucocyte images as linear or curvilinear uptake in the falx, tentorium cerebelli, or brain convexity. Assessment for such appearances should be made when evaluating whole-body radiolabeled leucocyte examinations in patients with WG. Correlative imaging with MR is suggested, because leucocyte imaging may underestimate the extent of meningeal abnormality. Leucocyte imaging may be useful as an adjunct to MR imaging in monitoring treatment response in patients with diffuse meningeal involvement by WG, as it may better identify active inflammation.

**References**