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## EDITORIAL

# PCP, AIDS and Nuclear Medicine

Two articles in this issue of the *Journal* deal with one of the most common complications of AIDS: *Pneumocystis carinii* pneumonia or PCP. In one, Katial et al. (1) describe a somewhat less common presentation of PCP on a <sup>67</sup>Ga scan. In the other, Goldenberg et al. (2) present the first clinical experience in AIDS patients using a radiolabeled antibody

specific for PCP. PCP frequently heralds the onset of AIDS in HIV-infected individuals. When AIDS was first recognized, PCP was the presenting opportunistic infection in 60% of cases (3) and occurred in over 80% of AIDS patients during the course of their illness. PCP has been and continues to be a significant source of morbidity and mortality in AIDS. It is the first diagnosis considered in a dyspneic or febrile AIDS patient and treatment is often begun empirically.

In the untreated patient, the typical clinical presentation of PCP in the

AIDS patient may be quite subtle with little more than a dry cough; fever or dyspnea occur commonly as well (4,5). The chest radiograph may be negative (6) or may show bilateral and diffuse interstitial markings, alveolar consolidation or “ground glass” opacities (7,8). Atypical unilateral infiltrates and cystic changes have been described also (8). These cystic changes have been related to an increased incidence of pneumothorax in these patients (9,10). Scintigraphic techniques, in general, are extremely sensitive for detection of PCP (6,11–

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14). The classic appearance of a  $^{67}\text{Ga}$ -citrate scan in PCP is that of intense, diffuse and homogeneous uptake throughout the lungs (15). Gallium-67 accumulation in the lungs in PCP has been related to the degree of neutrophil alveolitis accompanying the infection (16). An  $^{111}\text{In}$ -labeled autologous leukocyte scan may show a similar distribution of uptake (14) although not usually as intense. Technetium-99m-DTPA aerosol clearances are increased due to increased alveolar-capillary membrane permeability in PCP (12,17).

Because of the extremely high prevalence of PCP, routine clinical management of the AIDS patient often includes a prophylactic regimen of oral antibiotics (usually trimethoprim-sulfamethoxazole) or inhalation of aerosolized pentamidine in the attempt to prevent PCP. Prophylactic inhaled pentamidine reduces the relapse rate of PCP and reduces mortality from PCP (18). In recent years, this institution of PCP prophylaxis has changed clinical expectations (PCP is not always the first pulmonary opportunistic infection suspected in the patient on prophylaxis) and may change the clinical and radiographic presentation of PCP in the AIDS patient. The case reported by Katial et al. (1) in this issue reflects an altered presentation of PCP in a patient who had been treated with prophylactic aerosolized pentamidine. In this patient, the gallium uptake was limited to the lung bases. An aerosol scan sometime after treatment and resolution of the infection showed absence of activity in these areas. It is likely as the authors suggest that, like the  $^{99\text{m}}\text{Tc}$ -DTPA aerosol, the aerosolized pentamidine also failed to reach this portion of the lungs.

A focal or heterogeneous gallium uptake pattern may be becoming more common as clinicians become more adept at managing AIDS (11,19). Both prophylactic strategies and early aggressive treatment have become part of the approach to AIDS. Patients now are living long enough to experience repeated bouts of infection so that previously affected regions of the

lung which have incurred damage may be less hospitable to new PCP infection. The chest radiograph is more likely to show densities confined to or predominantly in the upper lobes (20), but localized infiltrates have also been reported (21). Cyst formation seems to be more common in patients treated with prophylactic aerosolized pentamidine (22). When chest radiographs are positive, the abnormalities will be restricted to the areas of the lung not reached by the inhaled aerosol. A nonhomogeneous or localized pattern of gallium uptake in the lungs may occur because other areas of the lung have been damaged by previous infections, because they are occupied by other disease, e.g., pulmonary Kaposi's sarcoma, as suggested in the patient described, because airway disease prevents uniform delivery of aerosolized medication (21) or simply because the aerosol is less efficiently delivered to the upper lungs (23). The yield of organisms with bronchoalveolar lavage in patients who have been given prophylactic aerosolized pentamidine is reduced as well (21).

The case report by Katial et al. also raises the issue of using aerosol scans for evaluating the uniformity of deposition of aerosolized medication. This has not been thoroughly described in the literature. Aerosol studies have been used to show that the delivery system used will affect the distribution of aerosol, either drug or radiotracer. Thus, the nebulizer used to deliver the radiopharmaceutical should be the same as that for the medication to ensure that the scintigraphic and therapeutic situations are similar. Aerosol scans are probably the best means available to us to predict retention of aerosolized medication and might be used to predict the dose needed to obtain effective prophylaxis. Aerosol scans show variable retention among patients who are candidates for aerosolized medication and the differences are not predicted by either a history of PCP or by pulmonary function tests. However, aerosolized pentamidine prophylaxis is most effective in those patients who have had no previous history of PCP (Bernard EM, Memo-

rial Sloan Kettering Cancer Center, *personal communication*).

Goldenberg et al. describe an exciting technique for specifically diagnosing PCP which has the potential to revolutionize the role of nuclear medicine in AIDS. Until now, nuclear medicine has offered extremely sensitive techniques for detecting opportunistic infections and neoplasms to which the issue of specificity was secondary. These techniques,  $^{67}\text{Ga}$ -citrate scans, radiolabeled leukocyte scans, aerosol clearance studies and, more recently, radiolabeled nonspecific human immunoglobulin (24-26), have offered methods for identifying the presence, site and/or extent of an opportunistic infection. In the more extensively studied techniques, some specificity can be obtained from the nature of the findings. For instance,  $^{99\text{m}}\text{Tc}$ -DTPA aerosol clearance is increased in the setting of PCP as well as in other AIDS-related conditions including cytotoxic alveolitis, cytomegalovirus pneumonitis, cryptococcosis and Kaposi's sarcoma. However, the magnitude of clearance increase is much greater in PCP than in the other entities. Rosso et al. found an 87% specificity for a clearance of  $>4.5\% \text{ min}^{-1}$  (12).

In  $^{67}\text{Ga}$  scans of the chest, a positive scan with a negative chest radiograph had an 85% specificity for PCP in a group of AIDS patients suspected to have PCP (6). In a less selected group of HIV-seropositive patients in whom an opportunistic infection was suspected and who were referred for  $^{67}\text{Ga}$  scans, as the intensity of pulmonary  $^{67}\text{Ga}$  uptake increased, the specificity of the scan for PCP increased from 79% with a 2+ scan to 95% for a 4+ scan (11). The pattern of  $^{67}\text{Ga}$  uptake in the lungs also may add specificity to the study. Uptake such as described in Katial et al.'s patient, i.e., occupying a significant portion of the lungs but not uniformly diffuse, has an 87% positive predictive value for PCP in the setting of AIDS. The "classic" homogeneous diffuse pattern in contrast had only a 64% positive predictive value (11). The relatively high positive predictive value of the kind of

pattern observed in the current case report is due most likely to the high prevalence of PCP in the HIV-seropositive population, and while the distribution of PCP infection in the lungs may be altered by prophylactic therapy, other infections are not affected. Nevertheless, until now good medical management of the AIDS patient has dictated that once a site of infection is localized either by radiography or by nuclear medicine techniques, a culture or biopsy should be obtained in order to make the specific diagnosis. Spontaneous sputum production is not very sensitive for PCP. While a positive sputum is significant, the absence of organisms in the spontaneously produced sputum is not very meaningful. Induced sputum has been used with a yield as high as 78% in some hands (7). In general, thorough evaluation for PCP has required performing fiberoptic bronchoscopy. The sensitivity of bronchoalveolar lavage for PCP has been reported as 86% and for transbronchial biopsy 87% (27). When the two techniques are combined, the sensitivity can reach 100% for PCP.

The need to make a specific diagnosis is all the greater because many of the opportunistic infections encountered in AIDS are difficult to treat. It is felt that the sooner appropriate and specific treatment is instituted, the more likely there is to be a response to therapy. Furthermore, the medications used to treat these infections tend to cause serious and intolerable side effects more often in the AIDS patient. Thus, although it is used in PCP, empiric therapy is less than optimal.

This makes the technique described by Dr. Goldenberg et al. (2) all the more interesting. They offer the potential to make a specific diagnosis of PCP noninvasively and within 24 hr. The idea is seductive and their results are encouraging. In a group of 15 evaluable patients with suspected or proven PCP and positive chest radiographs, the specificity of this technique was 87.5% with a very similar sensitivity (85.7%). Interestingly, the scans were positive even with ongoing therapy. This would mean that at least

empiric therapy for PCP need not be delayed while waiting for scan results. The paper raises a number of questions.

The first is what constitutes adequate demonstration of the *absence* of PCP. The combination of bronchoalveolar lavage and transbronchial biopsy offers the most sensitive tool (27). Although in the most capable hands, induced sputum may have a sensitivity of 78% for PCP, in the hands of most practitioners the sensitivity is considerably less (7). The sensitivity of conventionally obtained sputum is not adequate to confidently establish the absence of PCP infection. To some extent this calls into question the validity of the negative scan results in two or three patients in this series. Also, multiple types of opportunistic infections and neoplasms (e.g., lymphoma or Kaposi's sarcoma) may be present concurrently in AIDS patients. It would be interesting to know if this applied to any of the patients described in this report, and whether the inflammatory response related to other infections, especially vascular changes, influenced radiolabeled antibody fragment uptake. This does not detract from the importance of the current results, but it does identify issues which might be addressed in the extension of this work to a larger series of patients.

Another question raised by the authors themselves, is the wide range and sometimes long time intervals between definitive diagnosis (bronchoalveolar washings or transbronchial biopsy) and the performance of the PCP RAID scan. Also, since all patients were on therapy during the RAID scan and for variable intervals before, this introduces another confounding factor. The concurrent therapy, when it was effective, may have made the authors' results appear worse than they really were since it is possible that the infections may have resolved in one case before BAL/bronchoscopy. Undoubtedly, confident correlation of scan findings with diagnosis would benefit from close temporal relationship between the definitive diagnostic procedure and the RAID scan.

The fact that RAID scans were positive after a long period of therapy underscores the sometimes prolonged course of PCP in AIDS and the difficulty in adequately eradicating the infection (28,29). In one series reported, transbronchial biopsy demonstrated persistent PCP an average of 25 days after the institution of therapy (29) and in one instance, as long as 35 days after therapy was begun (28). Recurrence of PCP is seen in 20%–40% of patients (7). Our ability to noninvasively detect persistent PCP infections has not been thoroughly investigated. The significance of findings on a follow-up  $^{67}\text{Ga}$  scan, either positive or negative, has not been established. Technetium-99m aerosol clearance seems to revert to negative levels readily; again, the significance vis à vis adequacy of therapy and recurrence rates has not been well studied. Since RAID was positive *again* after a period of therapy in some of the patients, it is possible that RAID will be a useful means of demonstrating the adequacy of a course of therapy in AIDS-related PCP.

Where else will immunoscintigraphy for PCP fit into the evaluation of the HIV seropositive patient with a suspected opportunistic infection? The patients studied all had positive chest radiographs. How sensitive will immunoscintigraphy be in the setting of a negative chest radiograph? How will it compare to other techniques with which we are familiar, particularly  $^{67}\text{Ga}$  scanning or aerosol clearance studies? Will it detect extra-pulmonary PCP? Given the expected prevalence of PCP, immunoscintigraphy could be a first-line test in these patients. This will depend on the reliability of immunoscintigraphy in this setting. Ideally, further work-up would be necessary only once the RAID scan was negative. Only then would it be necessary to obtain a chest radiograph followed by either transbronchial biopsy or another less specific, more general nuclear medicine test like a  $^{67}\text{Ga}$  scan.

On the other hand, one also must keep an eye on the changing clinical picture of AIDS. As prophylaxis be-

comes more commonplace and effective, the choice of immunoscintigraphy for PCP might be less logical. Also, concurrent infections and neoplasms are not uncommon in AIDS. Once PCP is diagnosed, must we look further to exclude other opportunistic infections. Finally, as with all immunoscintigraphy, it will be important to determine the immunogenicity of this antibody fragment. Because PCP is a recurrent problem in these immunocompromised patients, we would like to be able to use a technique repeatedly.

We eagerly await the maturation of this technique. In the meantime, it behooves us as nuclear medicine practitioners to be aware of the variations in the findings in more conventional scintigraphic studies which are due to successful clinical intervention in AIDS. Similarly, we must be aware of any advances in clinical management which may affect the presentation of AIDS-related complications.

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