The Efficacy of Indium-111-Polyclonal IgG for the Detection of Infection and Inflammation

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The purpose of this study was to determine the efficacy of ^{111}In-polyclonal immunoglobulin (IgG) for the diagnosis of infection or inflammation. **Methods:** Fifty-three patients with suspected infection were prospectively studied. Each underwent an ^{111}In-polyclonal IgG study; biopsy, surgery, additional nuclear medicine scans and radiographic studies were used to confirm the IgG scan results. **Results:** The polyclonal IgG scan had a sensitivity of 97.9% and a specificity of 94% for infection or inflammation. When only infection or severe inflammation such as bowel infarction was considered, the sensitivity remained the same but the specificity fell to 83%. Chronic infections were detected equally as well as acute infections. Antibiotics, steroids, anti-inflammatory agents, diabetes and diminished renal function did not affect scan sensitivity. There were no adverse reactions to the radiopharmaceutical. Three patients underwent extended imaging. Their scans stayed positive for an average of 8 days. Three patients treated for infection had their scans turn negative on repeat study, confirming the efficacy of their antibiotic therapy. **Conclusion:** Indium-111-polyclonal IgG is an effective imaging agent of infection and/or inflammation that is useful in a variety of infections and in severe inflammatory diseases. The ease of preparation and safety make it an attractive alternative to labeled leukocytes.

Key Words: ^{111}In polyclonal human IgG; inflammation; infection

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Nuclear medicine techniques have an advantage over other imaging modalities in detecting occult infection because the whole body is imaged in one examination. Until recently, ^{67}Ga or ^{111}In-labeled leukocytes were the only radionuclide choices for imaging infection. Unfortunately, both have a number of disadvantages for infection imaging. Gallium has a poor target-to-background ratio, normal gastrointestinal uptake that can obscure abdominal abscesses, a 24–72-hr delay in diagnosis and poor specificity for infection (*1*). The latter is a problem in cancer and AIDS patients since gallium is taken up by a variety of tumors and other noninfectious processes (*2*).

Indium-111-labeled leukocytes have problems as well, the most important being the in vitro labeling process. Not only is the labeling process laborious, it requires a flow hood and other expensive equipment not readily available (*3*). Also, cells can become damaged during the labeling process if care is not taken (*3*). Finally, as Goodwin has pointed out, the most significant problem with in vitro labeling may be the possibilities of misadministering HIV-infected blood and the accidental infection of nuclear medicine personnel performing the labeling process (*4*). Other problems with ^{111}In-labeled leukocytes include the need for a 24-hr delay in imaging for maximal sensitivity, the low sensitivity for central skeletal infections and the question of effectiveness in chronic infections (*5–7*).

To overcome the above limitations, a variety of new radiopharmaceuticals is being developed, each with its own unique physiologic approach to localizing infection. Technetium-99m-HMPAO-labeled leukocytes, chemotactic peptides, nanocolloids, liposomes, streptavidin/biotin and monoclonal antibodies (Mabs) are all being investigated as possible agents for infection imaging (*8–14*).

Another new radiopharmaceutical under development is radiolabeled polyclonal immunoglobulin (IgG) (*15*). This material is available in kit form and does not require in vivo labeling. It has been shown to be effective against a variety of infectious organisms including gram-positive and gram-negative bacteria, *Mycoplasma pneumoniae*, *Pneumocystis carinii*, *Histoplasma capsulatum* and *Candida albicans* (*16*).

We undertook a prospective clinical study to determine the efficacy of ^{111}In-polyclonal IgG for detection of infection and severe inflammation. We determined the optimal imaging times and if delayed imaging improved sensitivity. We also studied the effects of antibiotics, steroids, anti-inflammatory agents, diabetes, decreased renal function and chronic infection on the sensitivity of the scan. Finally, we studied patients with positive scans to determine how long they remained positive and if the scan could determine the effectiveness of therapy.

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MATERIALS AND METHODS

The study was approved by the University of Utah Institutional Review Board. Adult patients were prospectively studied. Criteria for entry into the study required one of the following:

1. Fever of unknown origin defined as fever >100.5°F for 1 wk and no source identified by laboratory or physical examination after 1 wk.
2. Spiking or continuous fever of >100.5°F for 48 hr or longer and one of the following:
   - Increased white count × 2.
   - Two positive blood cultures for same organism with focal anatomic signs or symptoms.
   - Abdominal, pelvic or other localized pain for 1 day.
   - Focal skeletal or joint pain.
   - History of trauma or major surgery within last 3 wk.
   - Vascular graft or aneurysm.
   - Joint prosthesis.
3. Painful joint prosthesis with clinical suspicion of infection.
4. History of chronic inflammation or infection with continuing symptoms.
5. Clinical suspicion of a focal site of infection.

All patients who met the above criteria were studied except those with the following exclusion criteria:

- Known history of severe systemic reactions to human IgG.
- Known history of agammaglobulinemia or selective IgA deficiency.
- Calculated creatinine clearance of <40 ml/min.

For each patient entered into the study, we obtained a history, physical examination, list of current medications, pregnancy test (if applicable), routine blood chemistries, complete blood count with differential, urinalysis and sedimentation rate.

The radiolabeled human polyclonal IgG was prepared as follows. Human polyclonal IgG (Cutter Biologicals, Berkeley, CA) was complexed to the chelator diethylenetriamine pentacetic acid (DTPA) by R.W. Johnson Pharmaceutical Research Institute and supplied as a lyophilized solid in a single vial. Conjugation was by the Hnatowich procedure with DTPA bicyclic anhydride (*17*).

The labeling procedure was performed as follows. Two milliliters of sterile saline was added to a vial containing 2.0 mg of DTPA-IgG complex followed by 1.4–2.6 mCi of ^{111}InCl (10 mCi/ml). The mixture was then incubated at room temperature for 15 min. Three patients (51–53) were injected with a liquid PBS of DTPA-IgG supplied in a two-vial kit. To determine radiochemical purity, thin-layer chromatography was performed using ITLC silica gel impregnated glass fiber strips (Gelman Instrument Co., Ann Arbor, MI) with 2.5 ml of 0.1 *M* nonsterile citrate buffer as solvent. Labeling efficiency of 90% or greater was required.

The patients were injected over a 30-sec period with 2.0 mg of polyclonal IgG-DTPA labeled with 1.2 mCi/MBq of ^{111}InCl. Vital signs were monitored just prior to injection, and at 5, 15 and 30 min postinjection. Patients were instructed to drink 3–4 eight-ounce glasses of water during the first 6 hr following injection of ^{111}In-IgG.

Imaging was performed using a dual-headed large field of view camera equipped with medium-energy collimators. Digital whole-body images were obtained using 20% windows centered over the 172 and 247 keV photopeaks of ^{111}In. A matrix of 256 × 1024 was used. Additional spot views were obtained using a 256 × 256 matrix for a minimum of 4 min over the torso and 5 min over the extremities. In patients with lung activity, anterior and posterior upright spot images were obtained in addition to the routine views.

Single-photon emission computed tomography (SPECT) was also performed in selected patients. A three-detector dedicated SPECT system fitted with 280-keV medium-energy collimators was used. Two energy windows were set at 174 keV (20%) and 247 keV (15%). Images were acquired using a 64 × 64 matrix, 360° rotation with a noncircular body-contouring orbit, 120 stops for 45 sec/stop. Projection data were prefiltered with a Metz filter followed by reconstruction into transverse slices using a Butterworth filter (order 4, cutoff 0.2) and one-pixel-wide slices, followed by the generation of sagittal and coronal reformatting of image data.

Imaging was performed at 7.5 ± 1.5 or at 15 ± 3 hr (referred to as "early" scans) and again at 24 ± 4 hr postinjection. For patients for whom the images were negative or equivocal at 24 hr, 48 ± 4 hr imaging also was performed.

Patients who had positive scans on early and 24-hr images, who were not having surgical drainage and who were available for additional images, underwent extended imaging. Spot images of the positive area were obtained 3, 5, 8, 10, 12 and 14 days postinjection to determine how long the sites remained positive. Spot images of the abnormal areas were acquired for 15 min per view at 3 days, 25 min per view at 5 days and for 35 min on subsequent days.

Patients positive on initial scans who received antibiotic therapy and who were available for follow-up imaging underwent a second injection to determine whether the IgG scan was helpful in judging the effectiveness of treatment. The second scan was performed at least 9 days after the initial scan; the same imaging protocol was used as for the initial scans.

At completion of imaging, a second physical examination and a second set of laboratory tests identical to the pre-injection tests were performed to determine if the ^{111}In-IgG had caused any adverse effects.

The scans were read independently by three experienced observers, all of whom had participated in the original biodistribution and dosimetry studies of ^{111}In-IgG in 47 normal subjects; disagreements were settled by consensus. Any abnormal site of uptake outside the normal physiologic distribution was diagnosed as abnormal regardless of the degree of uptake or the timing postinjection. For determining overall sensitivity and specificity, all image sets on the same patient were read simultaneously; however, an additional set of readings was done to determine if the change in the appearance of the scan between the early and later images was useful for interpretation.

Confirmation of the results of the ^{111}In scan was determined by direct anatomical confirmation including surgery, biopsy, drainage, culture and autopsy; when anatomic data were not available, results of other diagnostic procedures such as leukocyte scan, bone scan, computed tomography, ultrasound and plain films were used. Tests could confirm the IgG scan if obtained within 2 days of the ^{111}In-IgG scan or if the patient was symptomatic at the time of the original IgG scan and when the confirmatory test was performed.

Based on direct anatomic confirmation and other confirming test results, each suspected infectious focus was categorized as true-positive, false-positive, true-negative, false-negative or unevaluable. Studies were unevaluable when too few data were available to establish the presence or absence of infection or if the confirming data were conflicting. When patients had multiple sites

of infection or inflammation, all sites were used to calculate the overall sensitivity and specificity.

In addition to determining the overall accuracy of ^{111}In-IgG for infection, we also determined the accuracy of IgG in select groups. These groups included patients receiving antibiotics, steroids, or anti-inflammatory agents; and patients with diabetes, diminished renal function (calculated creatinine clearance less than 60 ml/min) and chronic infections (those present longer than 14 days). The results in these groups were compared to those without the factor. Fisher's exact test was used to determine if the differences were statistically significant.

To determine if early images were as sensitive as delayed images, the 7.5- and 15-hr images were compared to 24- and 48-hr images. The McNemar test and the chi-square with continuity correction were used to determine if the differences were statistically significant. Changes in appearance of the scan between imaging times were also evaluated to determine if this was a useful criterion for interpretation. Scans which showed activity that stayed the same or increased in activity were considered positive; whereas, those which decreased in intensity were categorized as negative. Finally, to determine if upright chest images were useful, their sensitivity and specificity were compared to routine recumbent chest images.

RESULTS

Fifty-three patients were entered into the study (38 males (72%) and 15 females (28%)) with an average age of 52.6 yr (range 21–87 yr). Fifteen patients were immunocompromised, 15 had malignancies and 3 were leukopenic.

No adverse events immediately after injection and no alteration in the physical examination or laboratory tests were found that were not explainable by the patient's disease processes.

The overall sensitivity for infection or inflammation was 97.9% (46/47 sites) and the specificity was 93.8% (30/32 sites) (Table 1). One false-negative was in a patient with diverticulitis; two false-positives were cases of increased nonspecific bowel uptake. If only infection or inflammation severe enough to explain the signs or symptoms that motivated the patient's entry into the study were considered, the sensitivity remained at 97% but the specificity fell to 83.3% (30/36). In this group, six cases of uptake did not explain the patients' symptoms. In addition to the two cases of nonspecific bowel uptake, four cases of inflammation were detected: one case of heterotopic ossification, one uninfected hematoma, one uninfected decubitus ulcer and one case of uninfected postsurgical wound uptake.

All sensitivities in specific groups were calculated using the more stringent criteria for infection and inflammation. The sensitivity for 36 sites in patients on antibiotics at the time of the ^{111}In-IgG scan was 97.3% (36/37); this was not statistically significantly different from those not receiving antibiotics (100%, 6/6, $p = 1.00$). Similarly, there was no difference in sensitivity between patients receiving steroids (100%, 14/14) compared to those who were not (96.6%, 28/29, $p = 1.00$). Anti-inflammatory agents (100%, 20/20, $p = 1.00$) did not affect results. Neither diabetes (100%, 10/10) nor a creatinine clearance below 60 ml/min (100%, 9/9) affected sensitivity ($p = 1.00$). Finally, the chronicity of infection had no effect on IgG scan results. The sensitivity of the scan for infections greater than 14 days was 94.7% (18/19) compared to 100% for patients with infections less than 14 days old (24/24). These differences were not statistically significant ($p = 1.00$).

The sensitivity of the scan varied by imaging time. At 7.5 hr, the sensitivity was 81.5% (22/27), at 15 hr 100% (16/16) and at 24 hr 97.7% (42/43). The sensitivity at 7.5 and 15 hr was not statistically significantly different ($p = 0.181$); however, the differences between 7.5 hr and 24 hr were statistically significantly different ($p = 0.015$). Forty-eight-hour images were performed in 17 patients who were negative at 24 hr; none were positive.

Since images were obtained serially, changes in diagnoses and confidence levels can be examined between the early and late images. Seventeen of 31 sites (55%) imaged at 7.5 and 24 hr showed increasing target-to-background ratios; 13 sites (43.3%) did not change. One site showed decreasing activity over time. In 3 of 17 sites (17.6%), the change in activity from 7.5 to 24 hr was considered essential to making the diagnosis. In an additional 13 of 17 (77%), the change between early and late images increased physician confidence in the diagnosis. Five of 16 sites (28%) imaged at 15 hr and again at 24 hr showed increasing target-to-background ratios over time. In none of these cases was the change essential to making the diagnosis. In all five of these cases, physician confidence increased between the 15- and 24-hr views.

Seven patients showed increased lung activity on recumbent images on both the early and delayed images. In all, there was little change in activity between early and delayed images. In five of the seven, upright chest images caused the activity to significantly decrease, allowing a negative diagnosis. All these patients were confirmed not to have pulmonary infection or inflammation. Two patients showed no significant change between recumbent and upright images; both had confirmed chest pathology.

Extended imaging to determine how long the scan stayed positive without intervening treatment was performed in three patients. The scan remained positive for an average of 8 days (range 4–12 days). Three patients were reinjected after therapy to determine whether the scan was useful for judging the adequacy of treatment with antibiotics. All three were normal following antibiotic therapy for an average of 30 days (range 17–53 days).

Example cases of abnormal studies are shown in Figures 1–6.

DISCUSSION

Radiolabeled antibodies directed against tumor antigens were first used to diagnose metastatic disease over 35 yr ago (*18*). It wasn't until 1987 that radiolabeled immunoglobulins were first applied to infection imaging. Rubin et al. developed an ^{125}I-labeled murine monoclonal antibody to an epitope on *Pseudomonas aeruginosa*. To calculate

TABLE 1
Characteristics and Assessment of Patient Population

Patient no.	Final clinical diagnosis	Proof of diagnosis	IgG	Final assessment
1	Septic arthritis right hip	Culture	+	TP
	Renal transplant rejection	US, renal scan; response to treatment	+	TP
	No vascular graft infection	Spontaneous resolution without Rx	−	TN
2	Cellulitis right shoulder	CT, PE, response to Rx	+	TP
	Atonic bowel due to anticholinergics without infection	CT, KUB, long-term follow-up, response to Rx	+	FP
3	Heterotopic ossification left hip	Bone and leukocyte scans, long-term follow-up	+	TP
4	No empyema right lung base	CT, long-term follow-up	−	TN
5	Crohn's disease	Colonoscopy w/biopsy	+	TP
	No abdominal abscess	CT, long-term follow-up	−	TN
	No source of FUO	Unevaluable	−	Unevaluable
6	Lupus nephritis	Kidney biopsy	+	TP
	Lupus pneumonitis	CXR, response to Rx	+	TP
7	Brain abscess left parietal lobe	CT, surgical drainage, culture	+	TP
8	Cellulitis right distal tibia	Bone scan, x-ray, culture	+	TP
9	C. difficile colitis	Stool culture, response to Rx, CT long-term follow-up	+	TP
	No abdominal abscess	CT, long-term follow-up	−	TN
10	Pneumonia	CXR, CT, response to Rx	+	TP
	Nonspecific bowel uptake w/o infection	KUB, CT, stool culture	+	FP
11	No sternal osteomyelitis	X-ray, spontaneous resolution without Rx	−	TN
12	Chronic osteomyelitis left acetabulum and distal femoral prosthesis	Bone, leukocyte scan, response to Rx	+	TP
13	Osteomyelitis distal left femur	Left femur pin culture	+	TP
14	Osteomyelitis right foot	Bone scan, bone culture	+	TP
15	No right hip infection	Culture	−	TN
16	No lumbar spine infection	CT, long-term follow-up	−	TN
17	No left knee infection	Culture	−	TN
	Left knee hemangioma	Angiogram	+	TP
18	Crohn's disease without abscess	CT, response to Rx, long-term follow-up	+	TP
	Scrotal abscess	Culture	+	TP
	Bacterial pneumonia	CXR, response to Rx	+	TP
19	No source of FUO	Unevaluable	−	Unevaluable
	Heterotopic ossification of hips	Bone scan inconclusive	+	Unevaluable
20	C. difficile colitis	Stool culture, response to Rx	+	TP
	No brain abscess	MRI, long-term follow-up	−	TN
21	No vascular graft infection	Surgery, intraoperative culture	−	TN
22	No tuberculous meningitis	CSF culture	−	TN
23	Cellulitis of back	Culture, MRI	+	TP
24	Abscess left hip	Bone scan, culture, response to Rx	+	TP
	Rheumatoid interstitial lung disease	CXR, long-term follow-up	+	TP
25	Septic emboli left calf	Biopsy	+	TP
	No osteomyelitis T7 vertebra	Bone scan, long-term follow-up	−	TN
	Axillary graft infection versus dose infiltration		+	Equivocal
	Possible early cellulitis of back	CT inconclusive	+	Unevaluable
26	No liver abscess	Liver-spleen scan, long-term follow-up	−	TN
	No pneumonia	CXR, long-term follow-up	−	TN
	No source of FUO	Unevaluable	−	Unevaluable
27	Pyelonephritis right kidney	Urine culture, US, renal scan, response to Rx	+	TP
28	Infected prosthetic MTP joints	Joint culture	+	TP
	No osteomyelitis T12 vertebra	MRI, long-term follow-up	−	TN
29	Postoperative inflammation left foot	Bone scan, x-ray, long-term follow-up	+	TP
30	No cervical epidural abscess	MRI, long-term follow-up	−	TN
	Sinusitis due to intubation, endoscopies	X-ray, long-term follow-up	+	TP
31	No osteomyelitis left leg	Bone scan, x-ray, long-term follow-up	−	TN
32	No osteomyelitis skull	Bone scan, x-ray, long-term follow-up	−	TN
33	No osteomyelitis L3-4 vertebrae	Bone scan, long-term follow-up	−	TN
34	No diverticulitis	KUB, long-term follow-up	−	TN

TABLE 1
Continued

Patient no.	Final clinical diagnosis	Proof of diagnosis	IgG	Final assessment
35	No pelvic abscess	CT, long-term follow-up	–	TN
	Decubitus ulcer/inflammation R buttock	CT, response to Rx	+	TP
36	No infection right hip	Bone scan, long-term follow-up	–	TN
37	Hematoma w/inflammation right thigh	MRI, US	+	TP
	Sigmoid diverticulitis not identified	CT, barium enema	–	FN
38	Abscess left buttock	Surgery, culture	+	TP
	Postsurgical inflammation left BKA	Bone scan, long-term follow-up	+	TP
	Candidal cystitis	Urine culture	+	TP
39	No infection right distal femur	X-ray, long-term follow-up	–	TN
	No infection right hip	X-ray, long-term follow-up	–	TN
	Heterotopic ossification right femur	X-ray, long-term follow-up	+	TP
40	Right thoracotomy site inflammation	Bone scan, long-term follow-up	+	TP
	No evidence/disseminated coccidiomycosis	CSF and blood cultures, bone scan, long-term follow-up	–	TN
	Inflammation at buttock injection sites	Unevaluable	+	Unevaluable
41	No infection left hip	X-ray, long-term follow-up	–	TN
42	Sinusitis	X-ray, response to Rx	+	TP
	Osteomyelitis left tibia	Bone scan, response to Rx	+	TP
43	No empyema	X-ray, US, long-term follow-up	–	TN
44	No abscess T7-8 vertebrae	Bone culture	–	TN
45	Osteomyelitis left foot	Bone scan, x-ray, response to Rx	+	TP
	Cellulitis left leg	Bone scan, x-ray, PE, response to Rx	+	TP
46	Osteomyelitis right foot	Bone biopsy and culture	+	TP
47	Inflammation small bowel 2° to SMA thrombosis	Angiogram, surgery	+	TP
	Splenic infarct	CT, surgery	+	TP
48	Osteomyelitis right foot	Bone scan, surgery	+	TP
49	Discitis L2-3 vertebrae	Wound culture	+	TP
	Inflammation 2° to trauma and arthritis left foot	X-ray, long-term follow-up	+	TP
50	FUO due to drug reaction	Response to Rx, long-term follow-up	–	TN
	No pneumonia	CXR, long-term follow-up	–	TN
51	Osteomyelitis right mastoid	CT, bone scan, culture	+	TP
52	Osteomyelitis right hand	Bone scan, culture	+	TP
53	Osteomyelitis left foot	Bone scan, x-ray, culture	+	TP

BKA = below knee; CXR = chest x-ray; CSF = cerebrospinal fluid; CT = computed tomography; FUO = fever of unknown origin; KUB = abdominal x-ray; MRI = magnetic response imaging; MTP = metatarsal phalangeal; PE = physical examination; Rx = therapy; SMA = superior mesenteric artery; and US = ultrasound.

the degree of specific versus nonspecific antibody uptake, they compared their anti-*Pseudomonas* antibody with a nonspecific antibody against a nonmammalian, nonbacterial haptene, p-arsanilic acid (*19*). The uptake of the nonspecific antibody in infected sites was equal to the specific antibody. These researchers then switched from investigating Mabs to the development of radiolabeled human polyclonal IgG for detecting infection.

The mechanism of uptake of polyclonal IgG is not well understood. Possible mechanisms of uptake are outlined below.

Studies of the contribution of vascular permeability to IgG uptake have given conflicting results. Rubin et al. compared the uptake of ^{111}In-IgG to ^{99m}Tc-human serum albumin in animals with *Escherichia coli* abscesses (*20*). Uptake of ^{111}In-IgG in the infected site was higher than the albumin as early as 3 hr postinjection and continued to increase over 24 hr. Animals with collagen-induced arthritis also show higher accumulations of ^{99m}Tc-IgG than ^{99m}Tc-human serum albumin (*21*). Studies of patients with musculoskeletal infections have shown differences in the blood pool and delayed images with ^{99m}Tc-HDP versus ^{99m}Tc-IgG (*22*); this also points to a mechanism of uptake beyond increased vascular permeability. However, Oyen et al. found no difference in the degree of uptake between ^{111}In human serum albumin and ^{111}In IgG in rats with abscesses (*23*).

Human serum albumin is not the ideal agent to use for determining the degree of vascular permeability. The molecular weight of human serum albumin is approximately 69 KD, one-third that of nonspecific human immunoglobulin (169 KD). Using polymers of human serum albumin

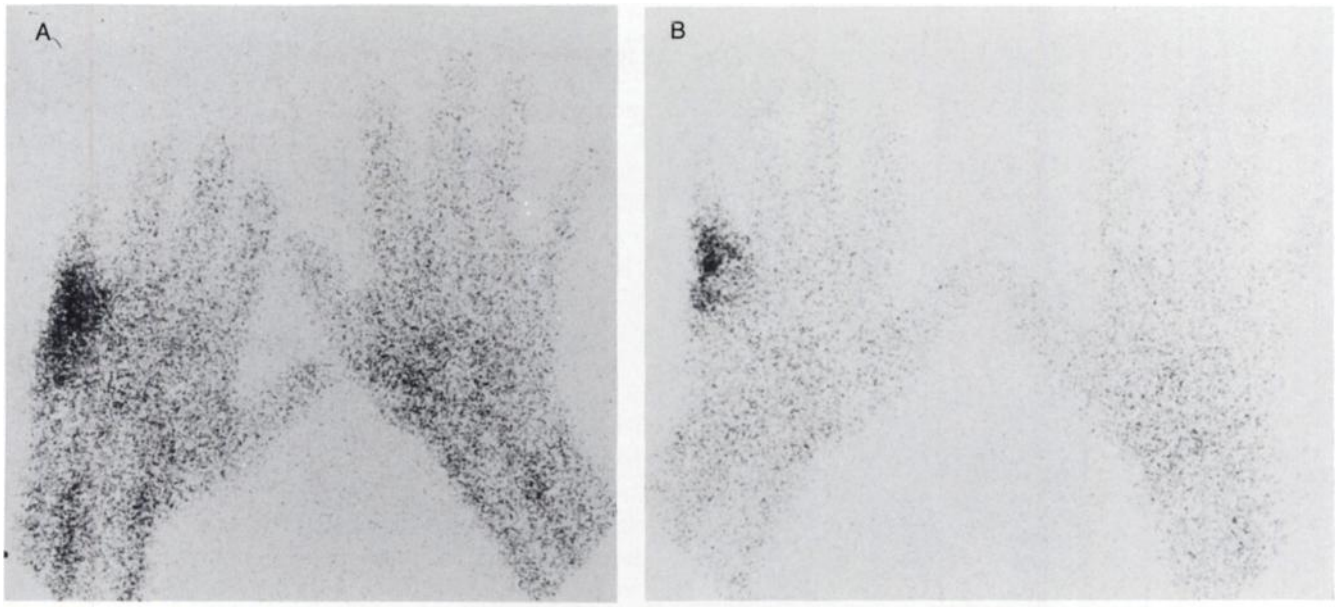

FIGURE 1. A 62-yr-old male with pain in the right hand (Patient 52). (A) Indium-111-polyclonal IgG image of the hands at 7.5 hr shows increased uptake in the right fifth digit. (B) Forty-eight hour image. Osteomyelitis was confirmed on biopsy and culture.

that are closer in molecular weight to human IgG, it was found that the target-to-background ratio for the human serum albumin polymers fell as the molecular weight increased (*24*). Thus, even studies that show equal uptake of human serum albumin and radiolabeled human IgG do not prove vascular permeability is the only mechanism involved in ^{111}In-IgG uptake; some other mechanism must account for at least a portion of the ^{111}In-IgG uptake.

Another mechanism proposed for polyclonal IgG uptake in infectious sites is binding of the antibody to Fc receptors on leukocytes at the inflammatory site. Studies by Fischman et al. showed that the whole antibody, Fc fragments or half Fc fragments showed significantly higher uptake than Fab′ fragments (*25*). Studies indicate pooled human IgG_1 binds to peripheral monocytes with high affinity ($K_a = 5 \times 10^{-8} M^{-1}$) onto 20–30,000 potential binding

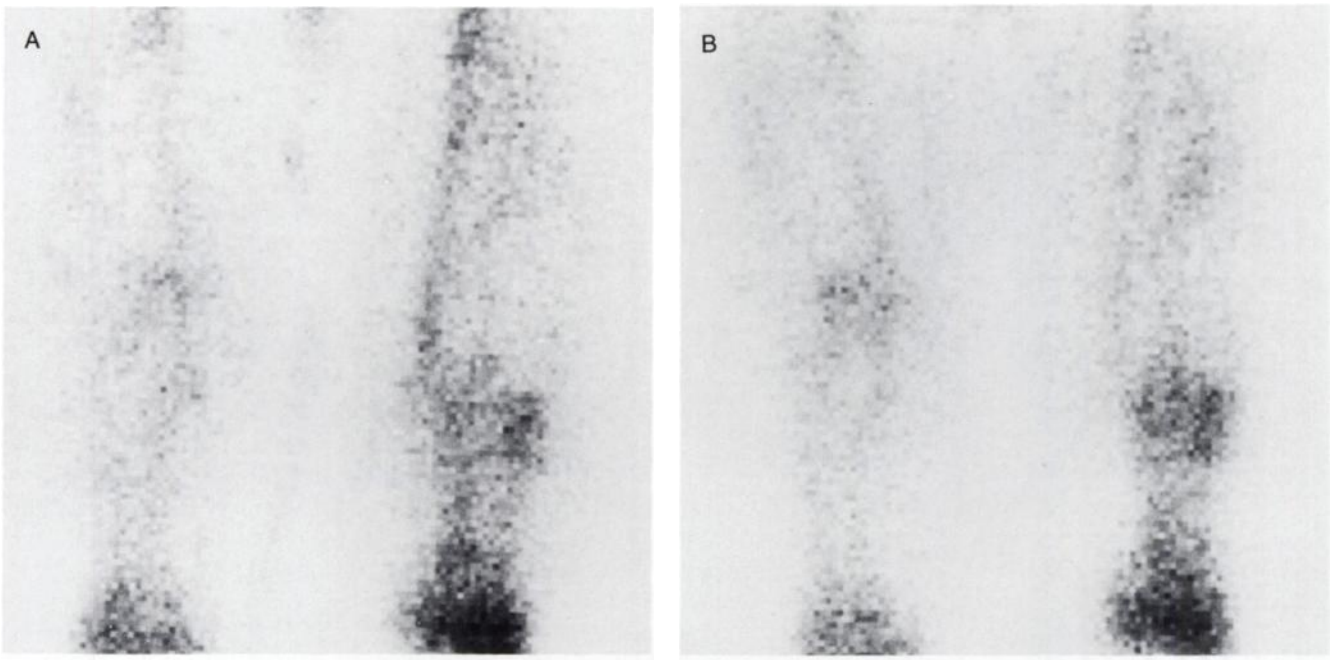

FIGURE 2. A 24-yr-old female with past fracture treated with internal fixation (Patient 13). She later developed osteomyelitis and was treated for 6 wk. She then developed new pain. (A) Indium-111-IgG scan over the femurs at 7.5 hr shows increased uptake at her previous fracture/osteomyelitis site in the distal left femur. (B) Twenty-four-hour view. Note that the diagnosis can easily be made on the earlier image. Osteomyelitis was confirmed by biopsy and culture.

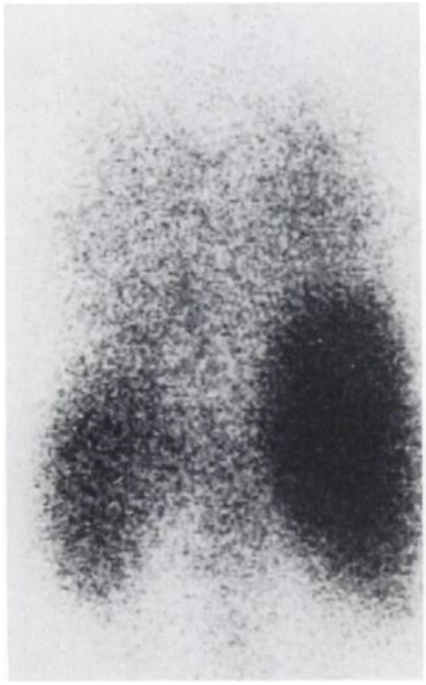

FIGURE 3. A 63-yr-old immunocompromised female with 2-wk history of fever of unknown origin (Patient 10). Posterior view of the chest at 24 hr shows diffuse increased uptake which was confirmed as pneumonia.

sites. Although binding to polymorphonuclear leukocytes occurs at a lower affinity ($K_a = 10^{-6}M^{-1}$), there are over 100,000 potential binding sites.

The evidence against Fc receptor binding is very strong. Neither competitive inhibition nor deglycosalating IgG to reduce Fc binding prevents antibody localization in inflammatory sites (*25*). Second, ^{99m}Tc-labeled Fc fragments show lower uptake in inflammatory sites than the whole antibody (*24*). Despite marked differences in Fc binding between the subclasses of IgG, animal studies show no difference in inflammation imaging ability (*25*). Autoradiographic studies indicate radiolabeled IgG is not associated with the cell fraction in inflammatory lesions (*26*). Finally, uptake of radiolabeled IgG is the same in leukopenic and normal animals (*25*). Clinical studies of patients with neutropenia have shown a high sensitivity for infection (*27*). These studies indicate that a physicochemical interaction of the antibody with leukocytes, rather than true antibody binding, is an unlikely mechanism of IgG uptake as well.

There is evidence that radiolabeled IgG binds to bacteria. The uptake of IgG is related to the number of bacteria in a site (*28*). Infections with strains of bacteria that contain high concentrations of Protein A, which is known to be capable of binding the Fc portion of antibodies, show higher uptakes of IgG than other strains. Unfortunately, the theory is based on Fc binding which does not seem to occur. In addition, sterile inflammation such as collagen-induced arthritis, show significant IgG uptake (*21*).

Finally, there is evidence that carrier protein and radiolabel chemistry play a part in the localization of radiolabeled IgG in inflammatory sites. A comparison of ^{111}In-IgG to IgA in infections showed significantly less uptake of the labeled IgA (*23,29*). Studies comparing different preparations of polyclonal IgG have shown there can be a significant difference in localization (unpublished data). Moreover, studies of IgG labeled with ^{111}In, ^{123}I and ^{99m}Tc indicate that the retention of radiolabeled IgG in abscesses varies in accordance with the radiolabel (*23*).

In our study, we were able to obtain surgical results in 25 patients; the remainder of the patients had infection or inflammation confirmed or excluded based on other imaging tests. This may affect the exact accuracy of the results, but this is the usual technique used to confirm the results of new imaging agents (*16,30*).

Our clinical results vary somewhat from those reported by Rubin et al. (*16*). They studied 128 patients and found a sensitivity of 91% and a specificity of 100%. Serafini et al. studied 40 patients and reported a sensitivity and specificity of 100% for polyclonal IgG (*30*). We also had a high sensitivity, but specificity varied according to the criteria we used to classify patients. When only infection or inflammation were considered, our specificity was 94%. If we classified patients as false-positives whose uptake was in sites not responsible for the patients' signs and symptoms, the specificity fell to 83%. For example, we correctly showed uptake in a hematoma. Although this area was associated with inflammation, we elected to classify the case as a false-positive since no infection was found and we did not feel the hematoma accounted for the patient's signs and symptoms. The numbers quoted for Serafini et al. above were based on any uptake in a site of infection or inflammation as a true-positive. Other investigators have recently reported a specificity for IgG closer to our results (*31*).

Polyclonal IgG is a nonspecific marker of inflammation

FIGURE 4. A 68-yr-old female with a 9-day history of abdominal pain and diarrhea (Patient 47). Anterior IgG image over the abdomen at 15 hr postinjection shows increased uptake in the bowel in the lower quadrants. At surgery, a necrotic small bowel was found secondary to superior mesenteric artery thrombosis.

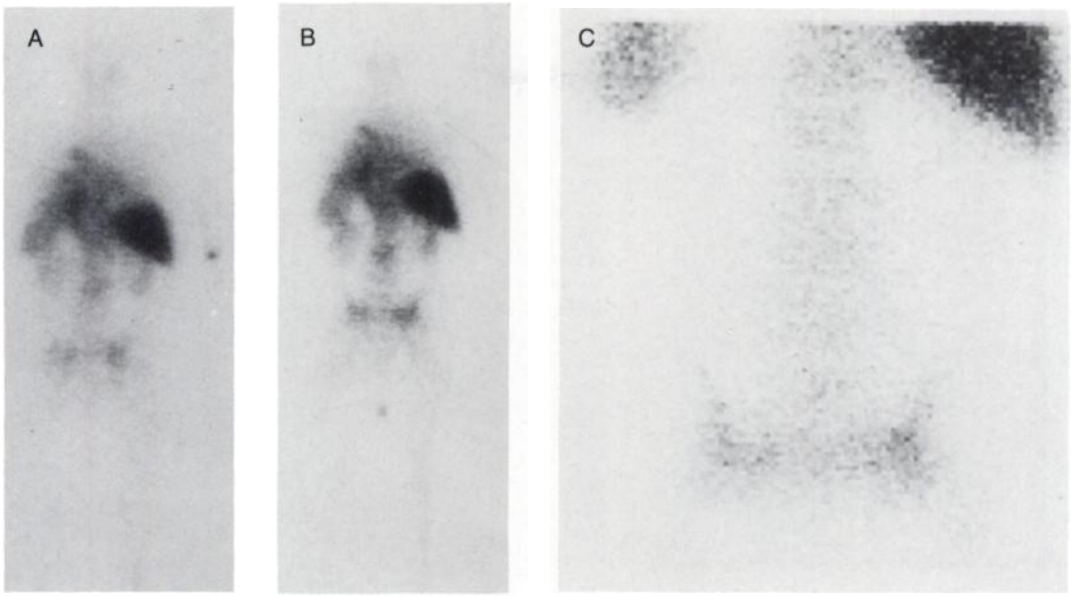

FIGURE 5. An 81-yr-old male with a 4-mo history of back pain and fever (Patient 49). (A) Posterior whole-body IgG scan 15 hr postinjection. Increased uptake is present in the upper lumbar spine. (B) Twenty-four hour posterior whole-body view again shows uptake in the spine. The patient was biopsied and discitis was found. He was treated with antibiotics for 10 days and a repeat scan was performed. (C) Repeat spot image over the lumbar spine shows clearing of previous activity.

rather than infection. Radiolabeled IgG uptake has been described in sterile abscesses, in collagen-induced arthritis, and in noninfected tumors (*32*). This situation is no different, however, than has been described for other infection imaging agents. Indium-111-labeled leukocytes have shown uptake in a variety of noninfectious diseases, including surgical wounds, ostomies, intramuscular injection sites, hematomas, inflammatory bowel disease, rheumatoid arthritis, tumors, adult respiratory distress syndrome, congestive heart failure, renal transplant rejection, cerebrovascular accidents, deep venous thrombosis, pulmonary emboli, pancreatitis, myocardial infarction, myocarditis, vasculitis, idiopathic pseudo-obstruction and following multiple enemas (*3,33*). Similar nonspecific uptake has been described for gallium, Mabs and nanocolloids (*32*). Uptake by ^{111}In-polyclonal IgG and other agents in sites of noninfectious inflammation can sometimes be helpful in identifying other sites of pathology.

Timing of imaging was important to obtain maximum sensitivity. By 24 hr, sensitivity was maximal. This is likely due to both a fall in background and increased uptake at the inflammatory site. We have reported similar findings for ^{111}In-labeled leukocytes. We found the sensitivity of ^{111}In-labeled leukocytes to be only 33% when imaged at 1–4 hr postinjection, but increased to 95% at 24 hr (*5*).

Diabetes, antibiotics, steroids and anti-inflammatory agents did not have any effect on the sensitivity of the IgG scan. All have been questioned as reducing the sensitivity of the ^{111}In-labeled leukocyte scan although our study of over 300 patients imaged with leukocytes did not find any statistically significant effect of diabetes or medications such as antibiotics and steroids (*34,35*). We also did not see any effect of chronic infection on the sensitivity of the scan. Again, some studies have indicated reduced sensitivity of ^{111}In-labeled leukocytes in chronic infections while others have not (*7,36*).

Azotemia in animals significantly reduces the sensitivity of IgG (*15*). We studied only patients whose creatinine clearance was over 40 ml/min; however, we did compare patients whose creatinine clearance was 40–60 ml/min to those above 60 ml/min and found no difference in sensitivity. We are currently studying patients with creatinine clearances less than 40 ml/min, and those on dialysis, to better determine the effect of diminished function on the sensitivity of radiolabeled IgG in humans.

Although the numbers are small, it appears the labeled IgG remains in the infectious site and does not wash out quickly as can occur with leukocytes labeled with ^{99m}Tc-colloid and HMPAO (*32*). Reinjection studies are also promising. Indium-111-IgG scans may be useful for determining the adequacy of antibiotic therapy. Further study, however, will be necessary to confirm these results in a large number of patients.

As mentioned in the introduction, radiolabeled polyclonal IgG has a number of potential advantages over other imaging agents such as ^{67}Ga- and ^{111}In-labeled leukocytes. First, polyclonal IgG is available in kit form and does not require in vitro labeling. This is a significant advantage over ^{111}In and ^{99m}Tc-HMPAO-labeled leukocytes. Both ^{111}In and ^{99m}Tc labels will be available in the future; however, even with the ^{111}In label, the dosimetry of IgG is better than with ^{111}In-labeled leukocytes. Diagnoses can be made as early as 7.5 hr with IgG. Gallium-67 often requires delays of 24–72 hr for a definitive diagnosis to be made. Studies of IgG in neutropenic patients have shown high sensitivity for infection (*27*). Neutropenia is a problem for leukocyte imaging (*32*). Finally, both bacterial and nonbacterial infections can be imaged, which is especially impor-

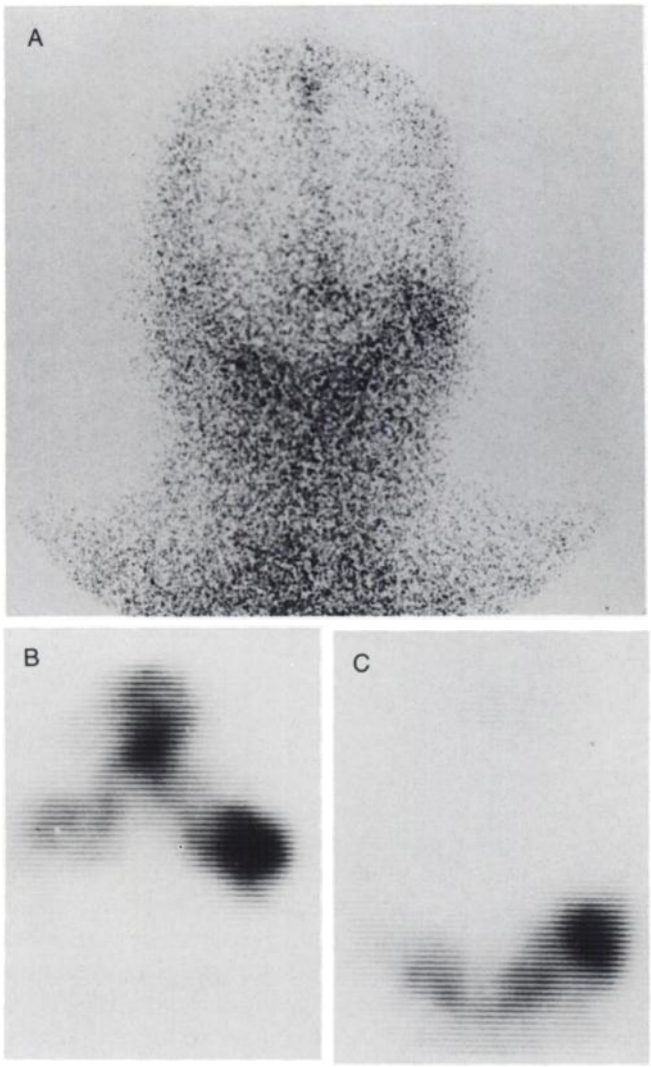

FIGURE 6. A 62-yr-old male with a 6-wk history of right facial pain and drainage from the right external auditory meatus confirmed to be mastoiditis (Patient 51). (A) Posterior skull view 48 hr after injection of ^{111}In-polyclonal IgG. Increased uptake is seen in the region of the right mastoid. (B) Transaxial SPECT view shows asymmetric activity in the mastoids. (C) Coronal SPECT view.

tant in immunocompromised patients (*16*). A potential disadvantage of IgG (at least in some cases), as noted in our study, is its uptake in both infectious and sterile inflammation.

In summary, we conclude that ^{111}In-polyclonal IgG is a sensitive technique for the detection of infection and inflammation. It has a number of advantages that make it an attractive alternative to labeled leukocytes.

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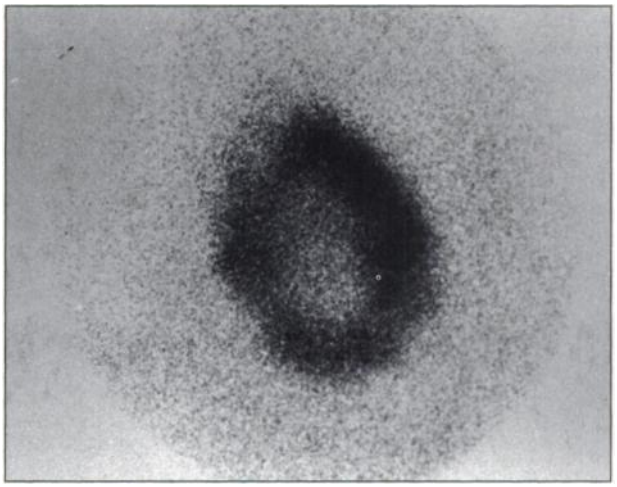
FIRST IMPRESSIONS

Thyroid Nodule Cystic Degeneration



PURPOSE
A 35-yr-old man presented with a large (5-cm) right thyroid nodule. He felt well and did not have any past history of thyroid problems or neck irradiation. Although he was clinically euthyroid, there was biochemical evidence of mild hyperthyroidism: serum T_4, 148 nmole/liter (normal 50-155); T_3, 3.9 nmole/liter (normal 1.3-3.0); ultrasensitive TSH undetectable (normal 0.6-6.0 mU/liter). Fine needle aspiration obtained fluid but no small malignant cells. A 4-hr RAIU was mildly elevated at 18%. A ^{99m}Tc-pertechnetate thyroid scan showed a large hyperfunctioning nodule in the right lobe of the thyroid with central cystic degeneration. The contralateral lobe is almost completely suppressed. The overall effect is to give the appearance of a myocardial perfusion scan.

TRACER
Technetium-99m-pertechnetate, 5 mCi (185 MBq)

ROUTE OF ADMINISTRATION
Intravenous

TIME AFTER INJECTION
15 minutes

INSTRUMENTATION
Siemens Lem (small field of view) camera and pinhole collimator

CONTRIBUTOR
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