SAMJ
ARTICLES

Gallium scintigraphy in the diagnosis and total lymphoid irradiation of Takayasu's arteritis

K. E. C. Meyers, P. D. Thomson, P. G. Beale, R. C. A. Morrison, U. K. Kala, D. W. C. Jacobs, D. Pantanowitz, R. H. Lakier, J. D. Esser

Takayasu's arteritis (TA) in children causes appreciable morbidity and mortality, predominantly as a result of the complication of renovascular hypertension (RVH).

Ten children with TA, complicated by RVH, were treated at our centre over the past decade. An initial raised erythrocyte sedimentation rate (ESR) and a purified protein derivative greater than 15 mm were present in every case. More recently, gallium scintigraphy has been used to demonstrate sites of active inflammation in affected vessels (3/4 patients) which became negative after total lymphoid irradiation (TLI). The latter was used in the last 6 children, and appeared to be effective in controlling disease activity as evinced in the normalisation of their ESRs and negative findings on gallium scintigraphy (in all 3 patients with prior active inflammation).

Because of vascular damage caused by the vasculitic process, surgical intervention is often required to improve organ perfusion, particularly of the kidney/s. Renal autografting (or allografting) seems preferable (6/11 kidneys functional) to renal bypass grafting (5/5 kidneys clotted). Patient survival improved when TLI was used in addition to standard surgical and medical therapy; this included steroids and antituberculous therapy with TLI, and steroids and cyclophosphamide in the two relapses. Five of 6 patients treated with TLI were alive after 32 - 54 months' follow-up, while 4 patients who received standard medical and surgical therapy but not TLI all died within 18 months of diagnosis.

Gallium scintigraphy is a helpful diagnostic tool in assessing vasculitic activity in TA; TLI is an important mode of immunosuppression, but still needs to be compared with cyclophosphamide as the major immunosuppressive.

S Afr Med J 1994; **84:** 685-688.

Departments of Paediatrics, Paediatric Surgery, Rheumatology, Surgery, Radiotherapy and Nuclear Medicine, University of the Witwatersrand, Johannesburg

K. E. C. Meyers, F.C.P. (S.A.)

P. D. Thomson, F.C.P. (S.A.)

P. G. Beale, F.C.S. (S.A.)

R. C. A. Morrison, F.C.P. (S.A.) (DECEASED)

U. K. Kala, F.C.P. (S.A.)

D. W. C. Jacobs, F.C.P. (S.A.)

D. Pantanowitz, F.C.S. (S.A.)

R. H. Lakier, M.MED. (RAD.)

J. D. Esser, M.MED. (NUC. MED.)

Takayasu's arteritis (TA) is a disease of undetermined aetiology, although an auto-immune component is strongly suspected.[1] The vasculitis in this disease is characterised by round-cell infiltration initially in the adventitial layers, with subsequent fibrosis of the vessel.[2] The aorta, proximal portions of its major branches, and the pulmonary arteries may be affected. Involvement of the renal arteries is not uncommon, resulting in stenosis or occlusion with subsequent renovascular hypertension (RVH). TA is an important cause of RVH in children,[3,4] and the hypertension has been shown to be related to a poorer outcome.[5] The outcome is often fatal, despite the combined use of immunosuppressive therapy and surgical intervention.[4-6]

Because of previous poor results from the PWV region,[6] we elected to use total lymphoid irradiation (TLI) in an attempt to control disease activity. TLI has been successful in controlling disease activity in another condition where vasculitis is a major component, i.e. systemic lupus erythematosus,[7] and as a preparation for renal transplantation.[8] We also elected to use auto-renal transplantation as opposed to the bypass grafting favoured previously because of the latter's poorer results. More recently, except where ESR was used as a measure of disease activity, gallium scintigraphy was used to show active vasculitis, as it has done in other diseases with a notable vasculitic component.[9-11]

Patients and methods

Thirteen children with TA were seen at our clinic over the past decade. There were 9 girls and 4 boys. Nine were black, 2 white and 2 of mixed race. Three patients have been excluded because of inadequate documentation. Four of the patients reported here (nos 1, 3, 4 and 7) have been described elsewhere.[4] All patients underwent transfemoral angiography and had serological tests for syphilis, double-stranded DNA, antinuclear factor, rheumatoid factor, anticardiolipin antibody and anti-neutrophil cytoplasmic antibody. They were also given 5 units of standard intradermal purified protein derivative (PPD) and the erythrocyte sedimentation rate (ESR) and serum creatinine levels were measured repeatedly. Direct tuberculous aortitis was investigated by culture of diseased vessels.[12] Corrective surgery was attempted in most patients (Table I).

Where available, specimens were submitted for histological examination. A polyclonal antimycobacterial antibody (anti-BCG) was used to identify a mycobacterial-like protein on vascular specimens submitted.[13] Gallium-67 citrate scintigraphy, which is useful for detecting sites of inflammation, was used pre-TLI in 4 patients (Table I). The patients received 185 MBq gallium-67 citrate intravenously and returned for scanning 24, 48, 72 and 96 hours later respectively. Initially planar anterior, posterior (Figs 1 and 2), lateral and oblique views were taken with a gamma camera; the lateral and oblique views were taken to avoid the superimposed uptake of central bony structures such as the vertebrae and sternum. Once the relevant gallium maps became available, the patients underwent single photon emission tomography (SPECT) scanning — coronal, transaxial and sagittal views.

TABLE I.
Takayasu's arteritis in children

No.	Ethnic origin	Sex	Age at presentation	Clinical and angiographic features	TA type	Evidence of tuberculosis	Initial ESR	Gallium scan		Surgical procedure	Other management					
								pre TLI	post TLI		Result	TB RX	S	TLI	Outcome	
1	White	Female	4 years	Hypertensive aortic stenosis plus bilateral RAS	II	PPD 4+	Raised	N/D	N/D	Right axillo-femoral bypass	C	Yes	Yes	No	D	HT
2	Black	Male	6 years	Hypertensive aortic stenosis plus bilateral RAS	II	PPD 4+ Brain granuloma	Raised	N/D	N/D	Died prior to surgery	–	Yes	Yes	No	D	HT
3	Mixed race	Female	4 years	Hypertensive abdominal and thoracic aortic aneurysms, bilateral RAS	III	PPD 4+ Positive family history	Raised	N/D	N/D	Right renal autotransplant	C	Yes	Yes	No	D	Bleed
4	Black	Female	9 years	Hypertensive abdominal aortic aneurysms plus bilateral RAS	II	PPD 4+	Raised	N/D	N/D	Bilateral aorto-renal bypass; left autotransplant	C P	Yes	Yes	No	D	Bleed
5	Black	Female	3 years	Hypertensive bilateral RAS	II	PPD 4+	Raised	N/D	NEG	Bilateral autotransplants; cadaver transplant 1989	C P	Yes	Yes	Yes	D	EBV
6	Black	Female	5 years	Hypertensive abdominal aortic stenosis plus bilateral RAS	II	PPD 4+ Positive family history	Raised	POS	NEG	Left autotransplant; mild RAS right	C	Yes	Yes	Yes	A	–
7	Black	Female	9 years	Hypertensive abdominal aortic stenosis plus bilateral RAS	II	PPD 4+	Raised	N/D	N/D	Bilateral aorto-renal grafts; cadaver transplant 1988	C P	Yes	Yes	Yes	A	–
8	White	Male	4 years	Hypertensive aneurysms of arch and thoracic aorta; bilateral femoro-popliteal involvement	V	PPD 4+	Raised	POS	NEG	No surgery (had dry gangrene of the toes)	–	Yes	Yes	Yes	A	–
9	Mixed race	Female	11 years	Hypertensive; diffuse arteritis of aortic arch, abdominal aorta, iliacs, right pulmonary, superior mesenteric and bilateral RAS	V	PPD 4+ Positive family history	Raised	NEG	NEG	Bilateral autotransplants	P	Yes	Yes	Yes	A	–
10	Black	Female	11 years	Hypertensive abdominal aortic and right renal artery stenosis	II	PPD 4+	Raised	POS	NEG	Right autotransplant	P	Yes	Yes	Yes	A	–

RAS: renal artery stenosis; TLI: total lymphoid irradiation; N/D: not done; POS: positive; NEG: negative; EBV: post-viral haemophagocytic syndrome; PPD: purified protein derivative; TB RX: tuberculous therapy; D: dead; A: alive; S: steroids; C: clotted; P: patent.
3 black patients, 2 male and 1 female, with incomplete documentation died. They had neither gallium scans nor TLI.

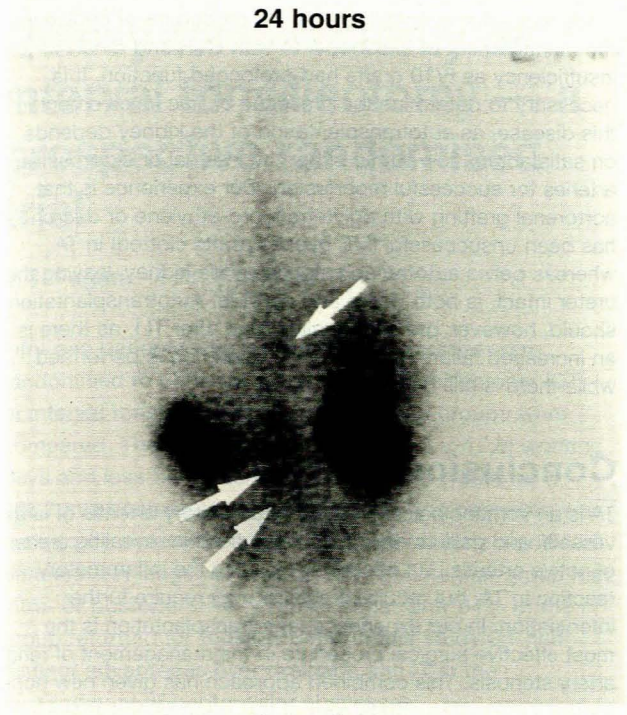

Fig. 1. Gallium-67 citrate posterior planar view of patient 8 pre-TLI at 24 hours. Uptake (white arrows) is demonstrated in the region of the descending thoracic abdominal aorta and the common iliac arteries.

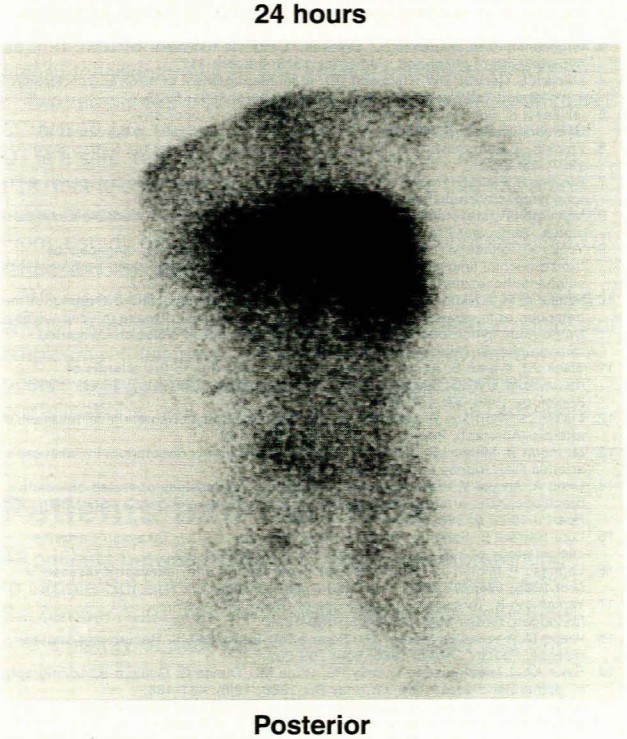

Fig. 2. Gallium-67 citrate posterior planar view of patient 8 post-TLI at 48 hours. All evidence of increased aortic uptake has disappeared.

Areas of positive uptake, disregarding normal bony uptake, were mapped anatomically to see if they conformed to a vascular structure; this positional relationship was subsequently confirmed with angiograms or computed axial tomography. This aspect of the project was initiated by one of the authors (R.C.A.M.).

TLI, in addition to steroids and antituberculous therapy, was used prospectively as a pilot study in patients 5 to 10 in Table I, following the previously poor results. Patients were treated with a wide-field low-dose irradiation schedule, an immunosuppressive preparation for renal transplantation[8] subsequently used in systemic lupus erythematosus patients.[7] TLI had not been used before to treat TA. Prior informed consent was obtained from the patients' legal guardians.

Patients were treated supine in the mantle position with cobalt 60; two or three matching fields were employed, usually at an extended source-skin distance. The fields extended from the base of the skull to 2 cm below the ischial tuberosities. The upper part of the humerus was treated as well as the whole chest, trunk and pelvis. Individualised blocks were constructed from half-value layer lead to shield lungs, kidneys and gonads. A dose of 8 Gy was given in 10 fractions of 0,8 Gy per fraction. Treatment was given anteriorly and posteriorly and all fields were treated at each session. Two fractions were given per week with at least 2 days between fractions.

Haematological indices were monitored with a full blood count and differential count before each treatment. TLI was interrupted if the rate of fall of platelet or white cells was excessive or if the total white cell count was less than 1,2 x 10^9/l, the neutrophil count less than 800 x 10^9/l or the platelet count less than 50 x 10^9/l. Treatment was also delayed if there was any evidence of infection.

Results

The 10 patients studied in detail are shown in Table I. They were classified into 5 types, the first 4 types as proposed by Ueno *et al.*[14] and modified by Lupi-Herrera *et al.*,[15] with type V (iliac involvement with or without other arterial disease) being added in 1988[6] (Fig. 3). Our patients were classified as follows: 7 had type II, I type III and 2 type V disease.

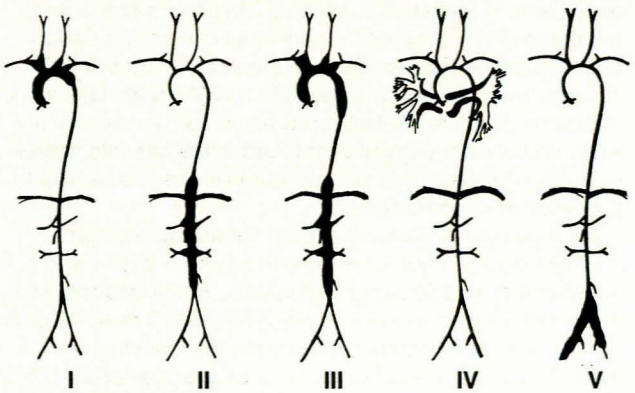

Fig. 3. Classification of TA into 5 types. The thick lines represent the regions involved. Note that type V disease includes iliac involvement alone (as demonstrated here), or in combination with one of the other types. (Reproduced with permission from Pantanowitz D. *Modern Surgery in Africa*. Johannesburg: Southern, 1988.)

On standard intradermal injection of 5 units of PPD, all patients initially tested strongly positive (PPD >15 mm). The initial ESR was also elevated in all 10 patients. All had evidence of RVH, renal insufficiency or both.[3,4,16]

The anti-BCG demonstrated mycobacterial-like protein expressed on spindle-shaped cells in the aortic wall of the TA patients tested. In addition, 3 patients had expression of class II major histocompatibility antigens on cells, demonstrated by monoclonal antibodies.[13] Gallium scanning before TLI was positive in 3 out of 4 patients and negative in all patients after TLI. A positive scan is indicated by increased uptake in the region of the major artery involved (Fig. 1). Following TLI, all 'hot areas' of uptake along the course of the actively involved arteries disappeared (Fig. 2). In the 6 patients given TLI, follow-up lasted 32 - 54 months with a median of 43 months. TLI halted disease progression as demonstrated on clinical examination, ESR and gallium scanning. Patients 8 and 9 have had disease activity flare up 12 months after TLI. This was successfully controlled with cyclophosphamide and steroids. Patient 5 died 20 months after TLI with severe unresponsive Epstein-Barr virus-induced post-viral haemophagocytic syndrome.

Renal autografting is preferred (6/11 functional) to renal bypass grafting (5/5 clotted). Patient survival improved when TLI was used in addition to standard medical and surgical therapy. Five of 6 patients treated with TLI were alive after 54 months' follow-up, compared with 4/4 who died within 18 months after standard medical and surgical therapy alone.

Patients 5 and 7 underwent successful allograft transplants after surgery to salvage their own kidneys failed.

Discussion

The diagnosis of TA in these patients was made on the basis of a combination of arterial insufficiency confirmed by angiography, positive activity tests, histological findings where available and gallium scanning. All patients demonstrated evidence of exposure to tuberculosis. The majority of the patients were black girls, in keeping with the findings of other studies.[3]

Gallium scintigraphy has previously been used to demonstrate areas of thrombophlebitis,[17] coronary aneurysms in Kawasaki's disease,[18] Wegener's granuloma,[9] renal glomerular disease,[19] cutaneous poly-arteritis nodosa[20] and congestive cardiac failure in rheumatoid arthritis.[11] We suggest that gallium scintigraphy is a useful technique in the diagnosis of active TA. Gallium is taken up by inflammatory cells, and since these cells are found in the affected vessels in TA, the uptake of this isotope is enhanced and highlights the areas of inflammation.

Management of TA is often both medical and surgical. Antituberculous drugs were used in all of our patients, whether they had active tuberculosis or not. Antituberculous treatment remains a controversial issue.[21] Until now, steroids, with or without cytostatics, have been the mainstay of medical therapy. This often controls progression of the disease only partially,[22] and TLI was therefore used in an attempt to minimise the probable cell-mediated injury in the vasculitis of TA. TLI has successfully controlled disease activity in each instance, although two late flare-ups occurred which required additional steroid and cyclophosphamide therapy.

We feel autotransplantation is the procedure of choice in the management of childhood TA with RVH and renal insufficiency as 6/10 grafts had prolonged function. It is necessary to determine the presence of iliac involvement in this disease, as autotransplantation of the kidney depends on satisfactory flow within either the internal or external iliac arteries for successful reperfusion. Our experience is that aortorenal grafting with polytetrafluoro-ethylene or dacron has been unsuccessful (5/5 bypass grafts clotted) in TA, whereas pelvic autotransplantation of the kidney, leaving the ureter intact, is both viable and durable. Autotransplantation should, however, preferably take place after TLI, as there is an increased failure rate when the operation is performed while there is still disease activity.

Conclusion

TA is an immunologically based inflammatory arteritis of large vessels, and gallium scintigraphy is useful in revealing areas of active arteritis. TLI effectively reduces the inflammatory reaction in TA, but recurrent activity may require further intervention. In our experience, autotransplantation is the most effective surgical procedure in the management of renal artery stenosis. This combined approach has given new hope for the long-term management of this often fatal disease in younger patients in our region. Whether steroids plus TLI or steroids plus cyclophosphamide are the best method of controlling disease activity, is being addressed in a randomised prospective study.

REFERENCES

1. Scott DGI, Salmon M, Scott DL, *et al.* Takayasu's arteritis: a pathogenetic role for cytotoxic T lymphocytes? *Clin Rheumatol* 1987; **5:** 517-522.
2. Isaacson C. An idiopathic aortitis in young Africans. *J Pathol Bacteriol* 1961; **81:** 69-79.
3. Wiggelinkhuizen J, Cremin BJ. Takayasu's arteritis and reno-vascular hypertension of childhood. *Pediatrics* 1978; **62:** 209-217.
4. Milner LS, Jacobs DW, Thomson PD, *et al.* Management of severe hypertension in childhood Takayasu's arteritis. *Pediatr Nephrol* 1991; **5:** 38-41.
5. Ishikawa K. Survival and morbidity after diagnosis of occlusive thromboaortopathy (Takayasu's disease). *Am J Cardiol* 1981; **47:** 1026-1032.
6. Franklin J, Pantanowitz D, Modiba M, *et al.* Takayasu's arteritis. *S Afr J Surg* 1987; **25:** 3-8.
7. Strober S, Field E, Hoppe RT, *et al.* Treatment of intractable lupus nephritis with total lymphoid irradiation. *Ann Intern Med* 1985; **102:** 450-458.
8. Myburgh JA, Meyers AM, Thomson PD, *et al.* Total lymphoid irradiation: current status. *Transplant Proc* 1989; **21:** 826-828.
9. Yuasa K, Tokitsu M, Goto H, *et al.* Wegener's granulomatosis: diagnosis by transbronchial lung biopsy, evaluation by gallium scintigraphy and treatment with sulphamethoxazole/trimethoprim. *Am J Med* 1988; **84:** 371-372.
10. Matsuura H, Ishikita T, Yamamoto S, *et al.* Gallium-67 myocardial imaging for the detection of myocarditis in the acute phase of Kawasaki disease (mucocutaneous lymph node syndrome): the usefulness of single-photon emission computed tomography. *Br Heart J* 1987; **58:** 385-392.
11. Slack JD, Walter B. Acute congestive heart failure due to the arteritis of rheumatoid arthritis; early diagnosis by endomyocardial biopsy; a case report. *Angiology* 1986; **37:** 477-482.
12. Milner LS, Morrison R, Jacobs D, *et al.* The role of mycobacterium in Takayasu's arteritis (Abstract). *Pediatr Nephrol* 1989; **3**(4): 192.
13. Morrison R, Milner LS, Jacobs D, *et al.* The role of mycobacterium in Takayasu's arteritis (TA). *Kidney Int* 1989; **35:** 913.
14. Ueno A, Awane Y, Wakabayachi A, Shimizil K. Successfully operated obliterative brachiocephalic arteritis (Takayasu's) associated with elongated coarctation. *Jpn Heart J* 1969; **8:** 538-543.
15. Lupi-Herrera E, Sanchez-Torres G, Marcushamer J, *et al.* Takayasu's arteritis: clinical study of 107 cases. *Am Heart J* 1977; **93:** 94-103.
16. Lagneau P, Michel JB. Reno-vascular hypertension and Takayasu's disease. *J Urol* 1985; **134:** 876-879.
17. Yamamoto K, Torizuka K. Clinical use of Ga-67 DFO-DAS-fibrinogen. *Radiat Med* 1987; **5**(5): 180-182.
18. Vargo TA, Huhta JC, Moore WH, Person DA, Edwards MS. Recurrent Kawasaki disease. *Pediatr Cardiol* 1986; **6**(4): 199-202.
19. Bakir AA, Lopez-Mazano V, Levy PS, Rhee ML, Dunca G. Gallium-67 scintigraphy in glomerular disease. *Am J Kidney Dis* 1988; **12**(6): 481-486.
20. Alexander JE, Seibert JJ, Lowe BA. Cutaneous uptake of Gallium-67 in polyarteritis nodosa. *Clin Nucl Med* 1987; **12**(11): 883-885.
21. Seedat YK. Primary arteritis of the aorta and its branches. *S Afr Med J* 1988; **74:** 71-73.
22. Shelhamer JH, Vokman JD, Parrillo JE, *et al.* Takayasu's arteritis and its therapy. *Ann Intern Med* 1985; **103:** 121-126.

Accepted 3 Aug 1993.