Supplementary Material

Prognostic Value of FDG-PET in a Prospective, Longitudinal Cohort of Patients with Large Vessel Vasculitis

Peter C. Grayson, MD, MSc[1], Sara Alehashemi, MD[1], Armin A. Bagheri, BS[1], Cahid Civelek, MD[2], Thomas R. Cupps, MD[3], Mariana J. Kaplan, MD[1], Ashkan A. Malayeri, MD[2], Peter A. Merkel, MD, MPH[4], Elaine Novakovich, RN[1], David A. Bluemke, MD[2], Mark A. Ahlman, MD[2]

[1] Systemic Autoimmunity Branch, National Institutes of Health, NIAMS, Bethesda, MD, USA

[2] National Institutes of Health, Clinical Center, Radiology and Imaging Sciences, Bethesda, MD, USA

[3] Division of Rheumatology, Georgetown University, Washington DC, USA

[4] Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, USA

Supplemental Table 1: Calculation of the PET Vascular Activity Score (PETVAS) of Arterial FDG Uptake

Arterial Territory	Qualitative Score
Ascending Aorta	0,1,2,3
Aortic Arch	0,1,2,3
Descending Thoracic Aorta	0,1,2,3
Abdominal Aorta	0,1,2,3
Right Carotid Artery	0,1,2,3
Left Carotid Artery	0,1,2,3
Innominate Artery	0,1,2,3
Right Subclavian Artery	0,1,2,3
Left Subclavian Artery	0,1,2,3

Note:

1. *To calculate PETVAS: Add the qualitative scores from each of the above specified 9 arterial territories. PETVAS range = 0 to 27.*
2. *Qualitative visual assessment of FDG uptake is performed in each arterial territory relative to FDG uptake in the liver: 0 = no FDG uptake; 1 = less than liver; 2 = equal to liver; 3 = greater than liver.*
3. *FDG uptake is not scored within areas of stent or graft placement but can be scored in an arterial territory containing a stent or graft if portions of the native artery can be visualized* within the territory.

Supplemental Table 2: Features of patients with clinically active LVV versus LVV in clinical remission

	Takayasu's arteritis		**Giant cell arteritis**	
Clinical Impression	***Active Disease***	***Remission***	***Active Disease***	***Remission***
No. patients	12	20	14	24
No. scans	15	29	25	42
Age Years (sd)	32.0 (9.6)	33.7 (11.5)	66.6 (9.9)	70.2 (9.0)
Female N (%)	10 (83)	13 (70)	10 (71)	17 (74)
Disease Duration Years (sd)	8.4 (9.3)	14.0 (10.4)	2.6 (2.5)	2.8 (2.6)
BMI *(kg/m^2)*	28.0 (7.1)	28.3 (9.8)	28.3(4.6)	28.1 (5.4)
ESR Mm/hr (sd)	26.9 (15.5)	16.7 (11.7)	25.6 (29.5)	17.6 (12.5)
CRP Mg/L (sd)	20.6 (25.8)	8.6 (18.0)	16.1 (28.2)	4.8 (5.8)
Fibrinogen Mg/dl (sd)	421.5 (133.0)	362.7 (100.9)	453.1 (125.9)	416.6 (81.5)
Endothelin-1 Pg/mL (sd)	4.6 (3.0)	5.6 (3.9)	4.6 (3.5)	4.4 (5.5)
Prednisone Yes (%)	10 (67)	15 (52)	14 (56)	27 (64)
Mg/day (sd)	12.1 (12.8)	5.7 (8.4)	13.7 (20.7)	8.2 (9.7)
Immune Meds Yes, (%)	9 (60)	24 (83)	18 (72)	18 (43)
Active PET scans (%)	12 (80)	14 (48)	23 (92)	26 (62)

Note: Some patients contributed multiple scans during both active disease and remission. SD = standard deviation; N= number; Immune Meds = any glucocorticoid sparing medication (e.g. methotrexate); Active PET scans = PET scan interpreted as consistent with active vasculitis by two independent nuclear medicine readers.

Supplemental Table 3: Clinical Features of Active Disease in 26 patients with LVV (Takayasu's arteritis = 12; Giant cell arteritis = 14)

Disease Feature	Prevalence (%)
Fatigue	17 (65)
ESR/CRP elevation	15 (58)
Headache	13 (50)
Arm claudication	11 (42)
Arthralgias/arthritis	7 (27)
Lightheadedness/Vertigo	6 (23)
Leg claudication	5 (19)
Polymyalgia rheumatica	5 (19)
Vision disturbance	4 (15)
Jaw claudication	3 (12)
Myalgia	3 (12)
Scalp tenderness	3 (12)
Carotidynia	2 (8)
Dyspnea	2 (8)
Heart failure	2 (8)
Hypertension	2 (8)
New vascular stenosis without symptoms	1 (3)

Supplemental Table 4: Diagnoses in the LVV Mimic Group

Final Diagnosis	Number of Patients
Behçet's disease	1
Fever of unknown origin - viral syndrome	1
Fibromuscular dypslasia	1
Iliac endofibrosis	1
Inflammatory arthritis	2
Headache / Complex migraine	3
Polyarteritis nodosa	5
Traumatic subclavian stenosis	1
Vasculopathy-associated immunodeficiency (e.g. DOCK8 deficiency)	2

Supplemental Table 5: Comparison of Qualitative FDG PET Scores by Arterial Territory and Disease

AORTA	Ascending Aorta		Aortic Arch		Descending Thoracic Aorta		Abdominal Aorta	
	Median diff	*P value*	*Median diff*	*P value*	*Median diff*	*P value*	*Median diff*	*P value*
GCA vs TAK	-0.02 (-0.55-0.51)	NS	0.16 (-0.37-0.69)	NS	0.08 (-0.45-0.61)	NS	0.53 (-0.01-1.06)	****
GCA vs Hyperlipidemia	0.81 (0.37-1.25)	****	0.72 (0.28-1.15)	****	0.86 (0.43-1.30)	****	0.93 (0.49-1.36)	**
GCA vs LVV Mimic	0.90 (0.28-1.25)	****	1.00 (0.38-1.61)	***	0.99 (0.38-1.60)	***	0.74 (0.12-1.35)	***
GCA vs Healthy	1.17 (0.32-2.02)	**	1.52 (0.67-2.37)	****	1.27 (0.42-2.12)	***	1.25 (0.40-2.10)	NS
TAK vs Hyperlipidemia	0.83 (0.27-1.39)	****	0.55 (-0.01-1.11)	NS	0.78 (0.22-1.34)	**	0.40 (-0.16-0.95)	NS
TAK vs LVV Mimic	0.92 (0.21-1.62)	**	0.83 (0.13-1.54)	*	0.91 (0.20-1.62)	**	0.21 (-0.50-0.91)	NS
TAK vs Healthy	1.18 (0.27-2.10)	**	1.36 (0.44-0.92)	****	1.19 (0.27-2.11)	**	0.72 (-0.20-1.64)	NS
Hvperlipid. vs LVV Mimic	0.09 (-0.55-0.73)	NS	0.28 (-0.36-0.92)	NS	0.13 (-0.51-0.76)	NS	-0.19 (-0.83-0.45)	NS
Hyperlipid. vs Healthy	0.36 (-0.51-1.22)	NS	0.80 (-0.06-1.67)	NS	0.41 (-0.46-1.28)	NS	0.32 (-0.54-1.19)	NS
LVV Mimic vs Healthy	0.27 (-0.70-1.24)	NS	0.53 (-0.44-1.49)	NS	0.28 (-0.69-1.25)	NS	0.51 (-0.46-1.48)	NS

BRANCH VESSELS	Carotid Arteries		Subclavian Arteries		Axillary Arteries		Iliac Arteries		Femoral Arteries	
	Median diff	*P value*	*Median diff*	*P value*	*Median diff*	*P value*	*Median diff*	*P value*	*Median diff*	*P value*
GCA vs TAK	0.44 (-0.09-0.97)	NS	0.46 (-0.07-0.99)	NS	0.64 (0.11-1.17)	**	0.65 (0.12-1.18)	**	0.89 (0.36-1.42)	****
GCA vs Hyperlipidemia	0.91 (0.48-1.35)	****	1.06 (0.62-1.50)	****	0.47 (0.03-0.90)	*	0.53 (0.10-0.97)	**	0.62 (0.18-1.06)	**
GCA vs LVV Mimic	1.24 (0.62-1.85)	***	0.88 (0.27-1.50)	***	0.24 (-0.37-0.85)	NS	0.33 (-0.28-0.95)	NS	0.37 (-0.24-0.98)	NS
GCA vs Healthy	1.47 (0.62-2.31)	**	1.49 (0.64-2.34)	****	0.68 (-0.17-1.53)	NS	1.33 (0.48-2.18)	***	1.01 (0.16-1.86)	*
TAK vs Hyperlipidemia	0.47 (-0.09-1.03)	***	0.60 (0.04-1.16)	*	-0.17(-0.73-0.38)	NS	-0.12(-0.67-0.44)	NS	-0.27(-0.83-0.29)	NS
TAK vs LVV Mimic	0.80 (0.09-1.50)	**	0.42 (-0.28-1.13)	NS	-0.40(-1.11-0.31)	NS	-0.32(-1.02-0.39)	NS	-0.52(-1.22-0.19)	NS
TAK vs Healthy	1.03 (0.11-1.95)	**	1.03 (0.11-1.95)	*	0.04 (-0.88-0.95)	NS	0.68 (-0.23-1.60)	NS	0.12 (-0.80-1.04)	NS
Hvperlip. vs LVV Mimic	0.33 (-0.31-0.96)	NS	-0.18(-0.82-0.46)	NS	-0.23(-0.86-0.41)	NS	-0.20(-0.07-1.67)	NS	-0.25(-0.89-0.39)	NS
Hyperlipid. vs Healthy	0.56 (-0.31-1.42)	NS	0.42 (-0.44-1.29)	NS	0.21 (-0.66-1.08)	NS	0.80 (-0.07-1.67)	NS	0.39 (-0.48-1.26)	NS
LVV Mimic vs Healthy	0.23 (-0.74-1.20)	NS	0.60 (-0.37-1.57)	NS	0.44 (-0.53-1.40)	NS	1.00 (0.03-1.97)	*	0.64 (-0.33-1.61)	NS

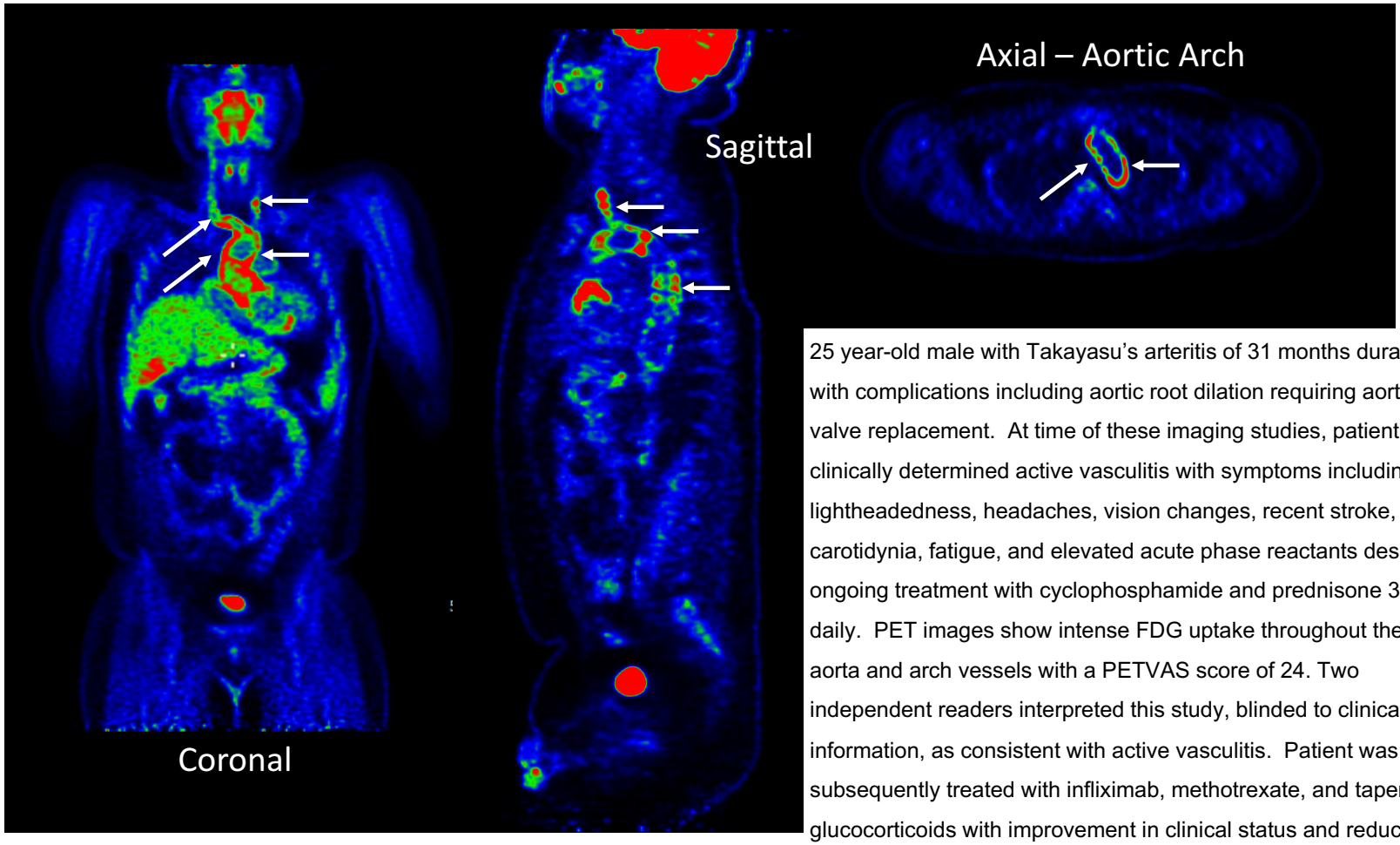
GCA = giant cell arteritis; TAK = Takayasu's arteritis; LVV = large-vessel vasculitis. * p <0.05; ** p<0.01; *** p<0.001; **** p<0.0001. ns = not significant.

Supplemental Table 6: Characteristics of Patients with LVV During Baseline Remission Visit

	Units of Measurement	**PETVAS ≥ 20** N=11	**PETVAS < 20** N=28	**P value**
PETVAS Score	Test range: 0-27	25 (21-27)	14 (6-19)	<0.01
Abnormal PET by Image Interpretation	n (%)	10 (91)	12 (43)	0.01
Disease Duration	Years	2.2 (1.0-8.9)	5.7 (0.9-37.9)	0.03
Follow up Time	Months	15.1 (3.3-20.4)	14.8 (4.3-27.8)	0.37
Type of Vasculitis *Takayasu's arteritis* *Giant cell arteritis*	n (%)	 1 (9) 10 (91)	 17 (61) 11 (39)	<0.01
Age	Years	63 (55-85)	47 (20-81)	<0.01
Sex	n (%)	8 (73)	18 (64)	0.72
Prednisone	mg/day	4 (0-25)	5 (0-30)	0.63
On Glucocorticoid-Sparing Medications	n (%)	3 (27)	20 (71)	0.03
ESR	mm/hr	15 (5-34)	17 (2-56)	0.80
CRP	mg/L	4.2 (0.2-32.8)	3.6 (0.2-46.6)	0.88
Fibrinogen	mg/dl	433.5 (204-573)	394 (155-554)	0.13
Endothelin 1	pg/mL	3.4 (1.5-7.3)	3.6 (1.2-13.7)	0.81
Clinical Relapse	n (%)	5 (45)	3 (11)	0.03
Features of Clinical Relapse	Descriptive	1. Const, mesenteric ischemia, ACPs 2. Const, new subclavian stenosis with arm claudication and loss of radial pulse 3. Const, PMR, ACPs 4. Const, PMR, ACPs, carotidynia 5. Const, arthralgias, ACPs	1. Pericarditis, ACPs, fatigue, arm claudication without angiographic progression 2. Const, pleuritis, ACPs 3. Const, ACPs	N/A

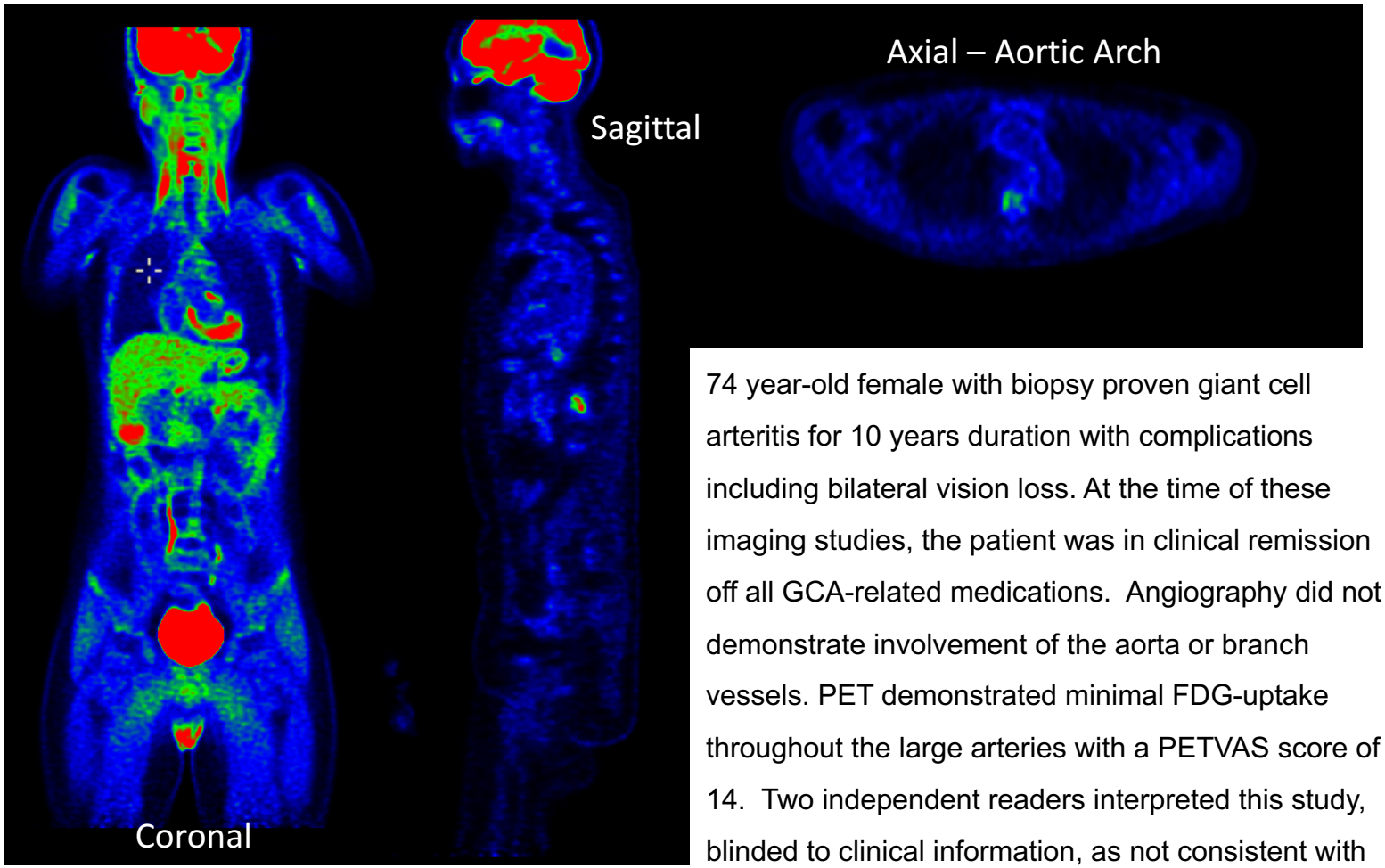
All continuous variables presented as median (range). ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Const = constitutional symptoms (fatigue, malaise, weight loss or fever); ACPs = elevated acute phase reactants; PMR = polymyalgia rheumatica. Mann Whitney U test and Fisher's exact test used to compare continuous and categorical data, respectively.

Supplemental Figure 1



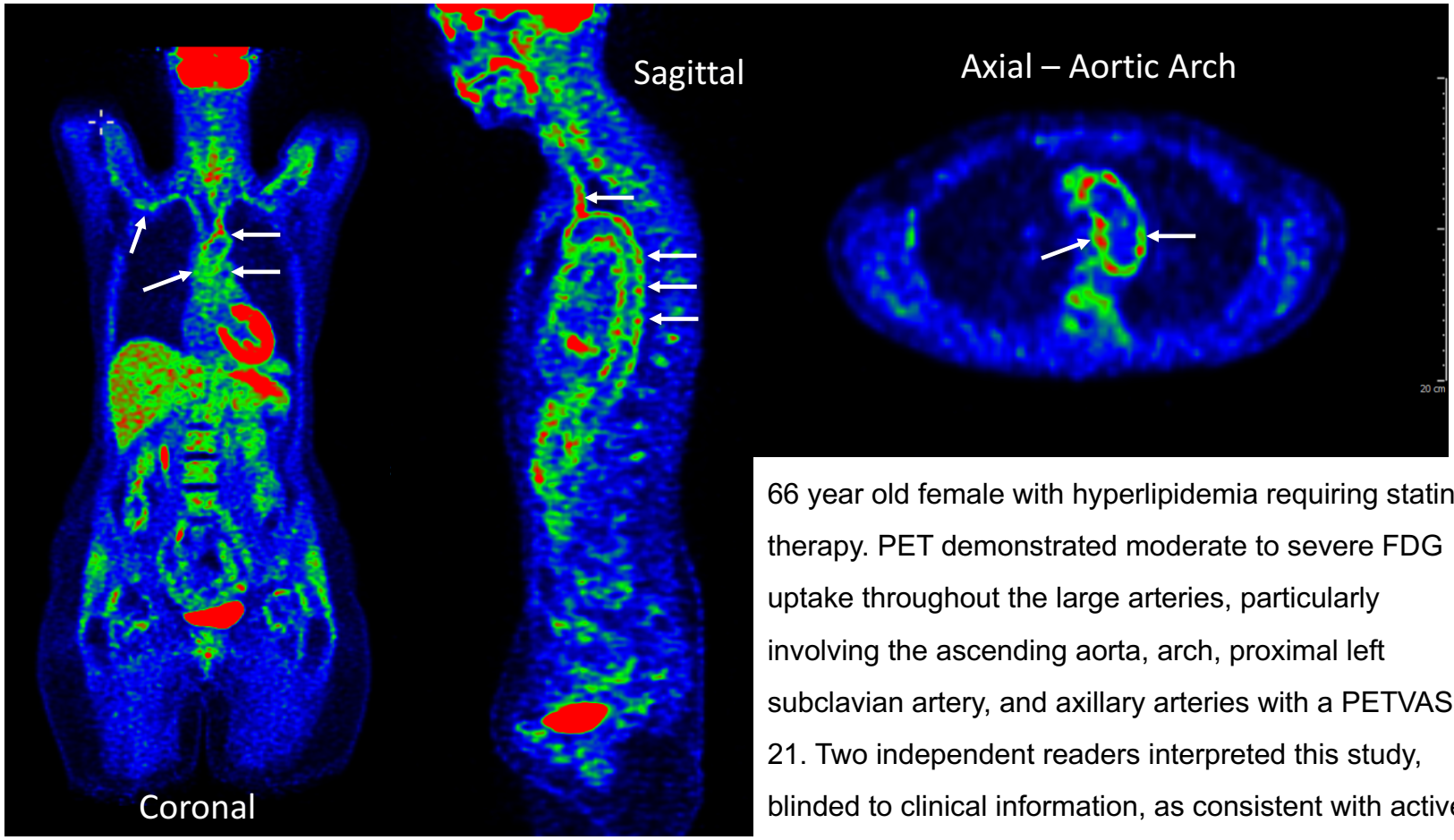
25 year-old male with Takayasu's arteritis of 31 months duration with complications including aortic root dilation requiring aortic valve replacement. At time of these imaging studies, patient had clinically determined active vasculitis with symptoms including lightheadedness, headaches, vision changes, recent stroke, carotidynia, fatigue, and elevated acute phase reactants despite ongoing treatment with cyclophosphamide and prednisone 30mg daily. PET images show intense FDG uptake throughout the aorta and arch vessels with a PETVAS score of 24. Two independent readers interpreted this study, blinded to clinical information, as consistent with active vasculitis. Patient was subsequently treated with infliximab, methotrexate, and tapered glucocorticoids with improvement in clinical status and reduction of arterial FDG uptake on 6-month follow-up imaging studies.

Supplemental Figure 2



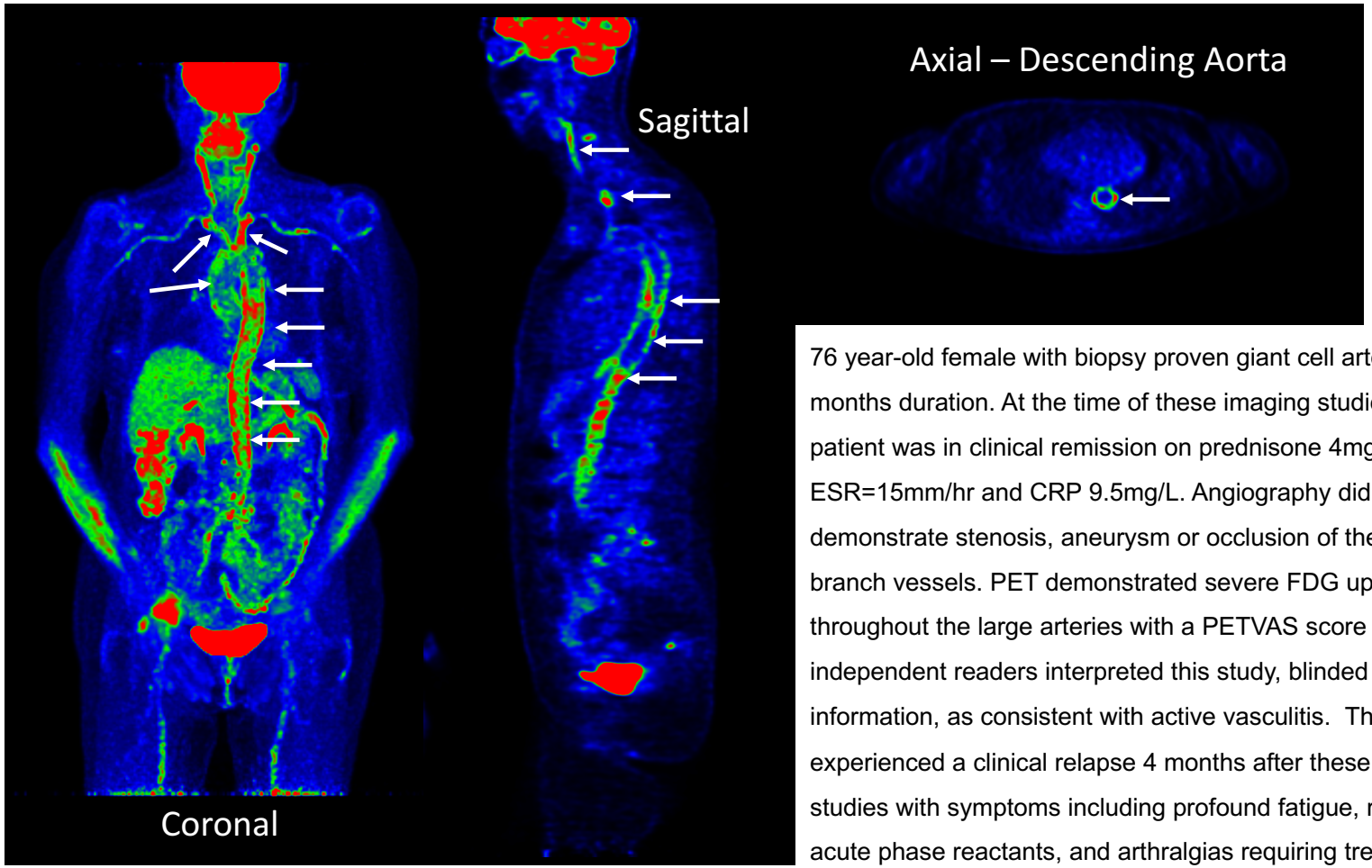
74 year-old female with biopsy proven giant cell arteritis for 10 years duration with complications including bilateral vision loss. At the time of these imaging studies, the patient was in clinical remission off all GCA-related medications. Angiography did not demonstrate involvement of the aorta or branch vessels. PET demonstrated minimal FDG-uptake throughout the large arteries with a PETVAS score of 14. Two independent readers interpreted this study, blinded to clinical information, as not consistent with active vasculitis.

Supplemental Figure 3



66 year old female with hyperlipidemia requiring statin therapy. PET demonstrated moderate to severe FDG uptake throughout the large arteries, particularly involving the ascending aorta, arch, proximal left subclavian artery, and axillary arteries with a PETVAS of 21. Two independent readers interpreted this study, blinded to clinical information, as consistent with active vasculitis.

Supplemental Figure 4



76 year-old female with biopsy proven giant cell arteritis of 17 months duration. At the time of these imaging studies, the patient was in clinical remission on prednisone 4mg/day with ESR=15mm/hr and CRP 9.5mg/L. Angiography did not demonstrate stenosis, aneurysm or occlusion of the aorta or branch vessels. PET demonstrated severe FDG uptake throughout the large arteries with a PETVAS score of 27. Two independent readers interpreted this study, blinded to clinical information, as consistent with active vasculitis. The patient experienced a clinical relapse 4 months after these imaging studies with symptoms including profound fatigue, rise in acute phase reactants, and arthralgias requiring treatment with increased glucocorticoids and methotrexate.