Pulmonary Manifestation (other than ILD) in Connective Tissue Disease

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Disclosures

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- Stills case (PAH)
- RA OB (airway disease)
- Cavitary lung disease GPA recurrence after renal transplant
- DAH

	ILD	Airways	Pleural	Vascular	DAH
Systemic sclerosis	+++	–	–	+++	–
Rheumatoid arthritis	++	++	++	+	–
Primary Sjögren's syndrome	++	++	+	+	–
Mixed CTD	++	+	+	++	–
Polymyositis/ dermatomyositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

The signs show prevalence of each manifestation (–=no prevalence; +=low prevalence; ++=medium prevalence; +++=high prevalence). ILD=interstitial lung disease. DAH=diffuse alveolar haemorrhage. CTD=connective tissue disease.

Table 1: **CTDs and common pulmonary manifestations**

Fischer A; Lancet 2012: 380

Case Presentation #1

- 38 y/o female diagnosed with Adult Onset Still's Disease 4/2020 (met Yamaguchi criteria [prolonged fever (103-104F) >1 month, profound myalgias/athralgias (arms>legs), N/V, diarrhea, nonprurutic rash (forearms/legs>face/torso), splenomegaly, abnormal LFT, negative ANA/RF]

4/2020 (initial diagnosis)	5/2020	7/2020	12/2020	4/2021	5/2021	11/2021
MTX and CS	+etanercept	(stopped etanercept) +sarilumab	(stopped sarilumab) +anakinra	MTX; CS; anakinra +COVID mRNA vaccine (#1 of 2)		MTX; CS; anakinra
Ferritin	65,000ng/mL			200ng/mL (just prior to COVID vaccine)	28,000ng/mL	5,524ng/mL (11/15) 18,179ng/mL (11/18)

Case Presentation

- Presented 11/2021 with progressive DOE and nonproductive cough spanning ~8 weeks, unresponsive to outpatient antibiotics
  - Elevated ferritin (5,524ng/mL), intermittent fever, relative tachycardia, “slight” rash on forearms, initial pulse oximetry 90% (room air)
  - Vitals Temperature 37.8C; BP 110/70; HR 107; RR 28; pox 96% 4 liters NC oxygen
- Echocardiogram 11/18/2021: small LV; flattened IVS (systole); LVEF 65%; severe RVE and reduced systolic function; TAPSE 1.6cm; DTI 9.3cm/s; moderately increased RV wall thickness; normal LA; mild RAE; estimated RAP 15mmHg; trace MR; mild-moderate TR; RVSP 77mmHg (assuming RAP 15); dilated IVC <50% change; small to moderate pericardial effusion without tamponade; 14% MV variation

Case Presentation

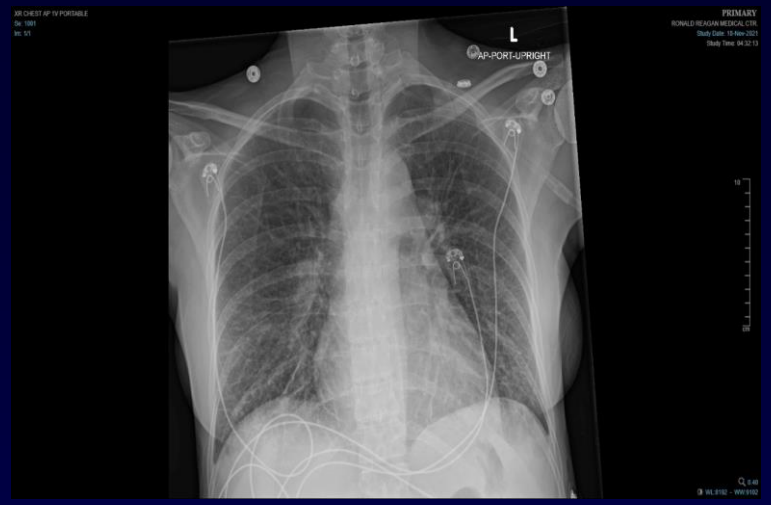
- RHC (11/17/2021): RAP 7; RV 70/1/13; PA 70/34/47; CO 4.2; CI 2.45; no response to iNO

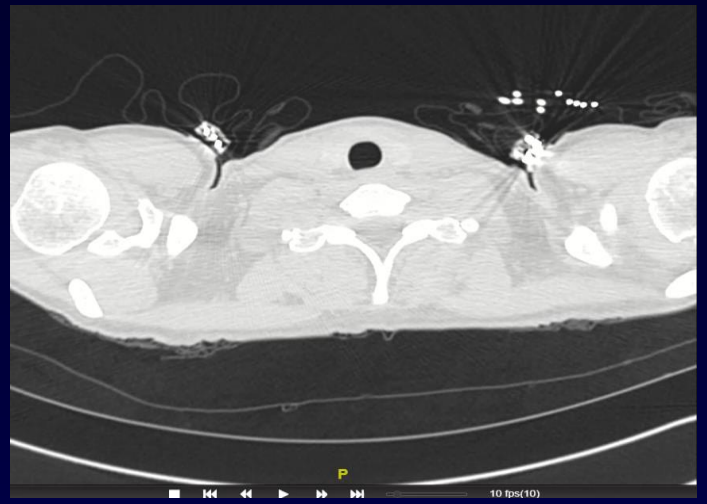
- Labs: troponin 0.04; WBC 3.8; Hgb 10.7; MCV 74.4; platelet 177,000; ESR 25; sodium 137; K 4.2; chloride 104; bicarbonate 22.8; BUN 10; creatinine 0.76; albumin 3.4; AST 112; ALT 29; alk phos 62; total bilirubin 0.4; LDH 1121; TSH 2.56; ferritin 5524; CRP 52.95; normal lactate; negative tox screen; negative pregnancy; negative U/A

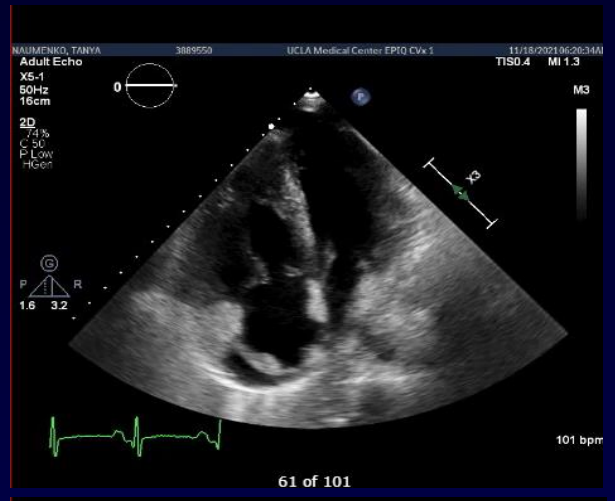
- Started on tadalafil and macitentan within 72 hours of presentation

11/18/2021

Ferritin 18,179 ng/mL
CRP 6.6 mg/dL
BNP 331 pg/mL
Troponin I 0.09 ng/mL

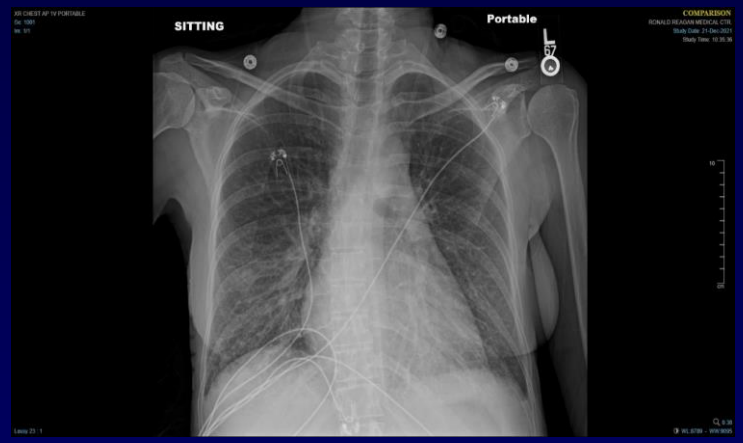


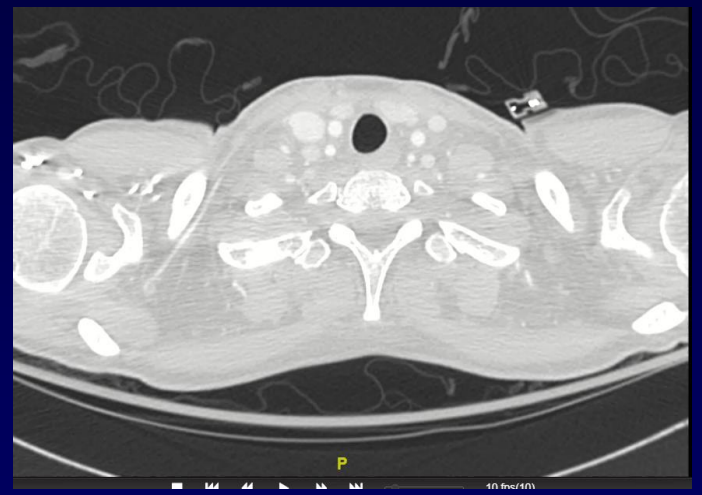


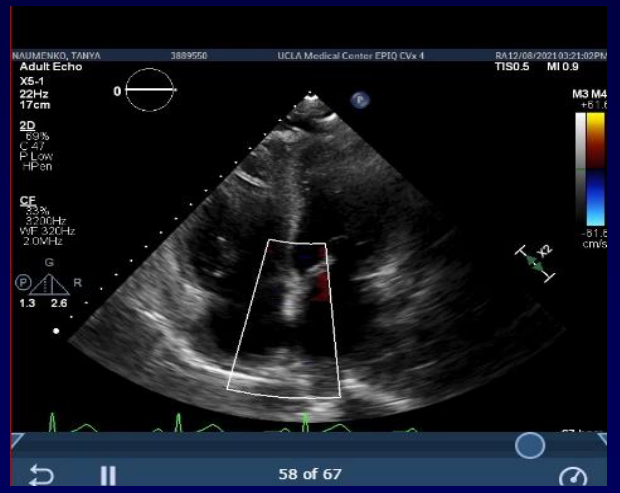


12/21/2021

Ferritin 38,820 ng/mL
CRP 2.2 mg/dL
BNP 229 pg/mL
Troponin I <0.04 ng/mL

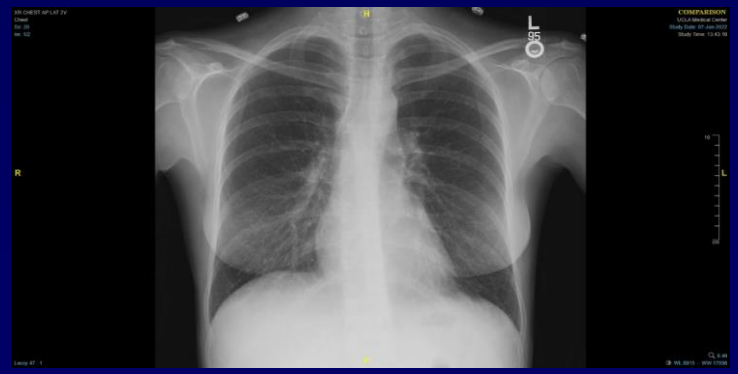


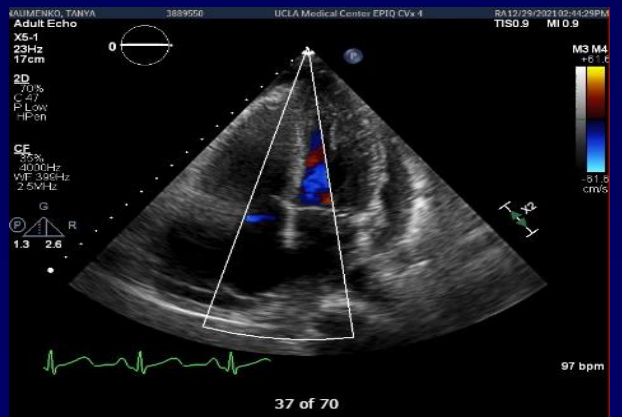




1/7/2022

Ferritin 6,711 ng/mL
CRP <0.3 mg/dL
BNP 117 pg/mL
Troponin I <0.04 ng/mL





Case Presentation *Clinical Course*

Date	11/23/2021	12/4/2021	12/7/2021	12/19/2021	12/29/2021	1/6/2021
Medical Regimen	Anakinra; CS; stopped MTX; started CSA; dose of rituximab given; HSV skin lesion and HSV 1 DNA +blood	-Concern for MAS; started etoposide and dexa; stopped CSA; changed anakinra to QID dosing	-tocilizumab #1 -etoposide #2 -Increased dexa to 30mg qday -intubated	-tocilizumab #2 -Etoposide #3 (12/11/2021) and #4 (12/21/2021) -extubated	Started ruxolitinib	-Decreased anakinra to BID -Dexa at 12mg qday
PH Regimen	Tadalafil (11/19) Macitentan (11/20)	→				
Ferritin	6,102ng/mL	101,160ng/mL	115,850ng/mL	15,212ng/mL	13,970ng/mL	7,066ng/mL
NK cell cytotoxicity	Reduced	Reduced				
Lumbar puncture		Increased protein				
IL2 soluble receptor			2x ULN			Just above ULN

Discussion

- AOSD (Adult onset Still's disease)
  - Incidence 1.6 cases per million (*rare*)
  - Monophasic, intermittent, chronic
  - Can be complicated by MAS (1.7% of AOSD cases)
  - Can be complicated by interstitial pneumonia, pleural effusion and/or transient pulmonary infiltrates

- 22 case reports (to date) describing PAH associated with AOSD
  - Appears to be associated with severe/persistent AOSD
  - Reported 22% mortality

Y. Hara et al; Respirology Case Reports 2021:9(5)
J. Narvaez et al; Seminars Arth & Rheum 2019:49(1)
Y. Nanke et al; Clin Exp Rheum 2007;25(2)

Discussion *SLE and PAH, and the concept of a corticosteroid responsive pulmonary artery vasculitis*

PRIMARY PULMONARY HYPERTENSION AND SLE

To the Editor: As Dr. Martin Wohl points out (N Engl J Med 288:204, 1973), patients with features of two or more connective-tissue syndromes present an interesting and puzzling clinical problem. The case discussed is almost identical to a patient whom we have recently seen with long-standing Raynaud's phenomenon, discoid lupus erythematosus, nondeforming arthritis and trophic ulcers with subcutaneous calcinosis. She died of progressive pulmonary hypertension associated with severe, painful, almost constant ischemia and cyanosis of the fingers. There was no clinical evidence of renal disease except a 1+ test for protein in the urine.

Although New Yorkers do not have any more success than Bostonians in resolving the clinical conundrum posed by patients with features of systemic lupus erythematosus (SLE) and scleroderma, some of our additional data may help. Our patient had high-titer

Clinical rheumatology, 1982, 1, N° 4, 301-304

Case Report

Corticosteroid responsive pulmonary hypertension in systemic lupus erythematosus

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In most of the cases, corticosteroids did not change the patient's condition and did not stop the continuous deterioration of the disease. There were only few reports of favourable results (14). Histologic examination of pulmonary vasculature in systemic lupus erythematosus suggested that there is an early inflammatory stage which is expressed as vasculitis (15). Subsequently, this changes into permanent and irreversible fibrosis. Corticosteroids may therefore have a beneficial effect on the inflammatory phase. We may therefore assume that the good therapeutic response of our patient points to the possibility that her disease was still in the inflammatory stage.

Table 1: Comparison of the catherization performed before the start of flucortolone and 2 months later

	Richt Atrial Pressure	Richt Ventricular Pressure	Pulmonary Artery Pressure	Mean Capillary Wedge Pressure	C.O.[1] lit/min	SVR[2]	PAR[3]	TPR[4]
1st catherization (before treatment)	7*	80/0–7*	100/40*	10*	5	1328**	800**	960**
2nd catherizarion (under flucortolone)	3*	50/0–8*	60/30*	15*	5.4	1333**	370**	592**

1 — C.O. = Cardiac Output (L/min)
2 — SVR = Systemic Vascular Resistance
3 — PAR = Pulmonary Arteriolar Resistance
4 — TPR = Total Pulmonary Resistance
* Pressure expressed in mmHg
** Vascular Resistance expressed in dynes/sec/cm^{-5}

Discussion

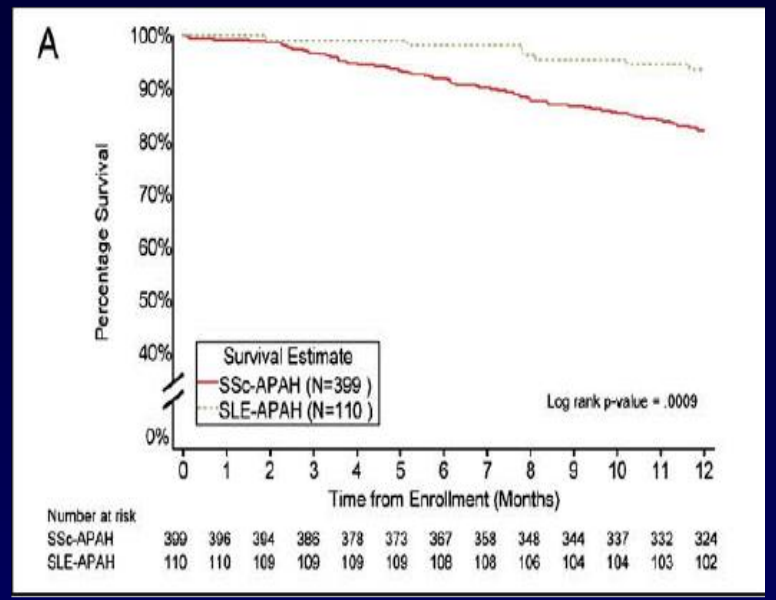
- In general, CTD-APAH more likely to receive immunosuppression than IPAH

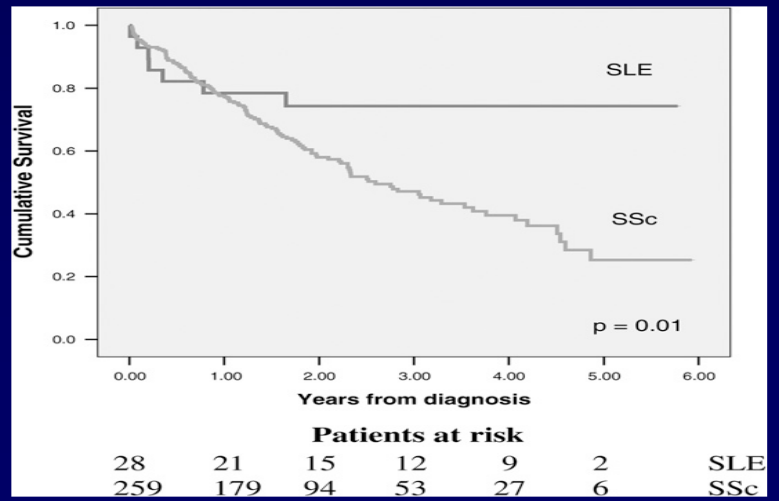
Table 3—*Pulmonary Arterial Hypertension-Specific and Immunosuppressive Therapies in Patients With CTD-APAH, IPAH, SSc-APAH, and SLE-APAH*

Therapy	Etiology: CTD-APAH (n = 620)	Etiology: IPAH (n = 1,196)	*P* Value, CTD-APAH vs IPAH	Etiology: SSc-APAH (n = 385)	Etiology: SLE-APAH (n = 107)	*P* Value, SSc-APAH vs SLE-APAH	*P* Value, SSc-APAH vs Non-SSc-APAH
Prostacyclin	225 (36.3)	561 (46.9)	< .0001	141 (36.6)	37 (34.6)	.7	.73
Endothelin-1 antagonists	310 (50.0)	563 (47.1)	.24	201 (52.2)	44 (41.1)	.04	.43
Phosphodiesterase inhibitors	312 (50.3)	597 (49.9)	.87	196 (50.9)	60 (56.1)	.34	.73
Combination therapy[a]	245 (39.5)	538 (45.0)	.03	159 (41.3)	40 (37.4)	.47	.59
Calcium channel blockers for PAH	58 (9.4)	140 (11.7)	.13	34 (8.8)	12 (11.2)	.45	.45
Immunosuppressants	74 (11.9)	15 (1.3)	< .0001	26 (6.8)	24 (22.4)	< .0001	< .0001
Cyclophosphamide	6 (1.0)	2 (0.2)	.01	5 (1.3)	0 (0.0)	.24	.12
Prednisone	10 (1.6)	5 (0.4)	.008	2 (0.5)	6 (5.6)	.0002	.001
Azathioprine	24 (3.9)	3 (0.3)	< .0001	12 (3.1)	6 (5.6)	.22	.18
Mycophenolate mofetil	25 (4.0)	2 (0.2)	< .0001	6 (1.6)	10 (9.3)	< .0001	< .0001
Methotrexate	10 (1.6)	4 (0.3)	.003	2 (0.5)	2 (1.9)	.17	.003

Values are No. (%). Non-SSc-APAH includes SLE-APAH, mixed connective tissue disease-APAH, and rheumatoid arthritis-APAH. PAH = pulmonary arterial hypertension. See Table 1 legend for expansion of other abbreviations.

[a]At least two PAH-specific medications, including prostacyclin, endothelin-1 antagonists, and phosphodiesterase inhibitors.





Chung L et al; CHEST 2010; 138(6)
Condliffe R et al; AJRRCM 2009; 179

Response to Immunosuppression

Table 3—*Comparison of Patients Who Responded and Did Not Respond to First-Line Immunosuppressive Therapy

Characteristics	Improved (n = 8)	p Value	Not Improved (n = 20)
Age, yr	32 ± 12		43 ± 18
Male/female gender, No.	1/7		4/16
SLE	5 (62)		8 (40)
MCTD	3 (38)		5 (25)
CREST	0 (0)		5 (25)
Other	0 (0)		2 (10)
NYHA functional class			
I	0 (0)	< 0.05	0 (0)
II	3 (38)	< 0.05	5 (25)
III	5 (62)	< 0.05	10 (50)
IV	0 (0)		5 (25)
6-min walk distance, m	294 ± 118†		240 ± 107‡
Mean right atrial pressure, mm Hg	5 ± 3		7 ± 5
mPAP, mm Hg	49 ± 16	34 ± 11	51 ± 12
Cardiac index, L/min/m^2	3.1 ± 0.5	3.5 ± 0,5	2.6 ± 0.7
PVR index, Wood U/m^2	15.6 ± 4	10.1 ± 4	21.4 ± 8
SvO_2, %	68 ± 9	69 ± 15	65 ± 8

*Data are presented as No. (%) or mean ± SD unless otherwise indicated. CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia.

Responder defined as patients with NHYA FC I/II with sustained hemodynamic improvement after at least one year of immunosuppressive therapy (cyclophosphamide and CS)

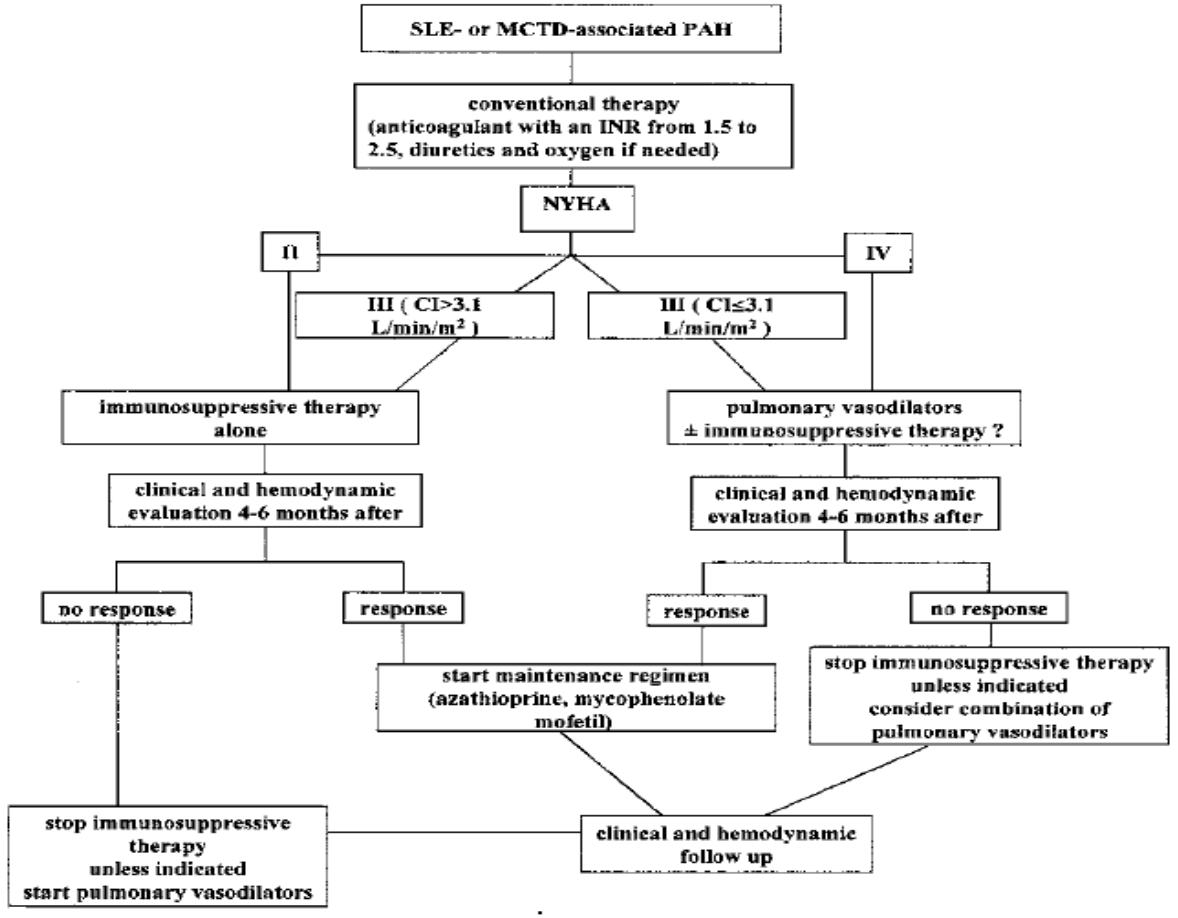


Figure 2. Proposed algorithm for treatment of patients with systemic lupus erythematosus (SLE)– or mixed connective tissue disease (MCTD)–associated pulmonary arterial hypertension (PAH). Responders to immunosuppressive therapy were defined as patients in New York Heart Association (NYHA) functional class I or II with hemodynamic improvement after the last pulse of cyclophosphamide. This algorithm must be read with caution because it relies on retrospective and open-label data and must therefore be confirmed by future randomized controlled trials. INR = international normalized ratio; CI = cardiac index.

O. Sanchez et al; CHEST 2006;130
X. Jais et al; Arth & Rheum;58(2)

PAH and inflammation

Modern Age Pathology of Pulmonary Arterial Hypertension

Elvira Stacher[1,2,3], Brian B. Graham[3], James M. Hunt[3], Aneta Gandjeva[3], Steve D. Groshong[4], Vallerie V. McLaughlin[5], Marsha Jessup[5], William E. Grizzle[6], Michaela A. Aldred[7], Carlyne D. Cool[3], and Rubin M. Tuder[3]

[1]Institute of Pathology, Medical University of Graz, Graz, Austria; [2]Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria; [3]Program in Translational Lung Research, Division of Pulmonary Sciences and Critical Care Medicine, Anschutz Medical Campus, Aurora, Colorado; [4]Department of Pathology, National Jewish Hospital, Denver, Colorado; [5]University of Michigan Health System, Cardiovascular Center, Ann Arbor, Michigan; [6]Department of Pathology, University of Alabama, Birmingham, Alabama; and [7]Genomic Medicine Institute and Taussig Cancer Institute, Cleveland Clinic and Department of Genetics, Case Western Reserve University School of Medicine, Cleveland, Ohio

What This Study Adds to the Field

The current work systematically examines the largest assortment of lungs collected from transplanted patients with idiopathic and associated pulmonary arterial hypertension in the past 2 decades. Our study reveals that in patients with advanced disease, there is a distinct spectrum of pulmonary vascular and nonvascular pathologies, including localized interstitial and perivascular inflammation. In this set of patients, who were enrolled for lung transplantation while being treated with the modern armamentarium of drug therapies, the appearance of classical pulmonary vascular lesions related to the disease was unaffected. Our results provide a unique insight into the spectrum of these pathological alterations, which can inform future translational work.

Safety and Efficacy of B-Cell Depletion with Rituximab for the Treatment of Systemic Sclerosis–associated Pulmonary Arterial Hypertension

A Multicenter, Double-Blind, Randomized, Placebo-controlled Trial

Roham T. Zamanian[1,2*], David Badesch[3], Lorinda Chung[1,4], Robyn T. Domsic[5], Thomas Medsger[5], Ashley Pinckney[6], Lynette Keyes-Elstein[6], Carla D'Aveta[6], Meagan Spychala[6], R. James White[7], Paul M. Hassoun[8], Fernando Torres[9], Andrew J. Sweatt[1,2], Jerry A. Molitor[10], Dinesh Khanna[11], Holden Maecker[1], Beverly Welch[12], Ellen Goldmuntz[12], and Mark R. Nicolls[1,2,13*]; on behalf of the NIH ASC01 Study Group

E. Stacher; AJRRCM 2012;186(3)
R. Zamanian AJRCCM 2021;204(2)

Conclusions

- AOSD may be associated with PAH and this PAH may respond to immunosuppression +/- PAH-specific therapy (similar to Lupus)

Case Presentation #2

- 61 year old woman with seropositive (RF+/CCP-) rheumatoid arthritis diagnosed in 2002, hypothyroidism, pulmonary hypertension diagnosed on RHC 7/2013, bilateral pulmonary embolism 9/2013, and obstructive lung disease (never smoker).
- In 2002, symmetric polyarthralgias and significant stiffness in her hands, knees, hips
  - Initial medrol dose packs
  - methotrexate 15 mg qweek from 2002-2004
  - hydroxychloroquine and ibuprofen
  - At some point, transitioned MTX to leflunomide 20 mg daily and continued hydroxychloroquine 200 mg BID
  - late 2013, she noticed hard nodules concerning for rheumatoid nodules on her right hand, left elbow and legs; consideration of abatacept (orencia) but not eventually done

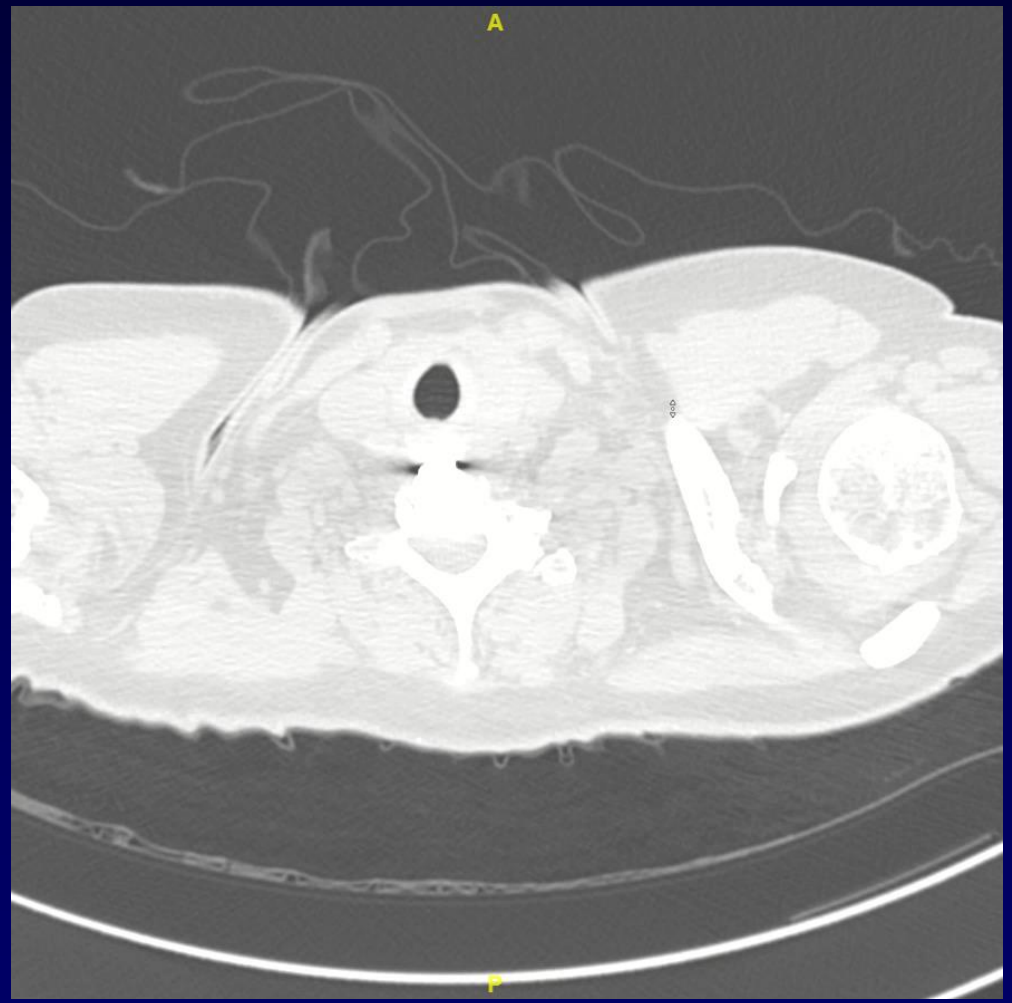
Bilateral Heart Catheterization

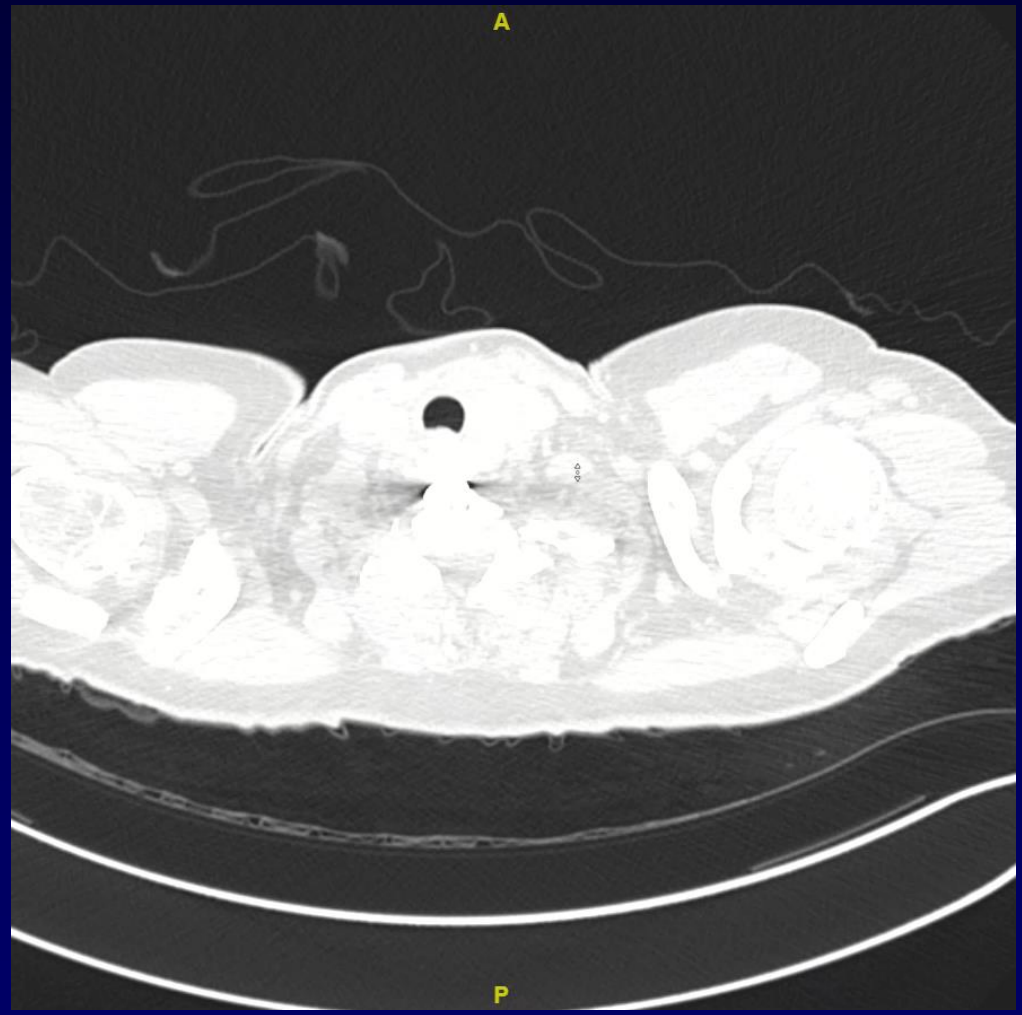
- Right heart catheterization and left heart catheterization with coronary angiogram, July 18, 2013 (Henderson, Nevada): RA 22, RV 78/22, pulmonary capillary wedge 16, PA pressure 78/31 with a mean of 51, cardiac output 2.75. Cardiac index 1.45 (thermodilution), PA saturation 54%. Arterial saturation 92% (on room air); PVR 14.9 wood units. Left heart coronary angiogram with nonobstructive CAD

Pulmonary Function Testing

- 04/21/14 (Baseline): FVC 3.0 (82%), FEV1 1.98(70%), FEV1/FVC 66, FEF 25-75 1.08 (43%), TLC 4.96 (91%), DLCO 21.17 (84%)
- 11/04/15: FVC 3.15(92%), FEV1 1.92(73%), FEV1/FVC 61, FEF 25-75 0.92(39%), TLC 5.92(115), DLCO 21.1(87.9)
- 09/23/16: FVC 2.45(73%); FEV1 1.84 (72%); FEV1/FVC 75; FEF 25-75% 1.46(64%)
- 08/07/17: FVC 2.92(86%); FEV1 1.85(72%); FEV1/FVC 64; FEF 25-75% 0.87(38%); TLC 5.52(107%); RV 2.72(136%); DLCO 20.43(86%); no BD response
- 7/30/2018: FVC 3.12(93.3%); FEV1 1.87(73.1%); FEV1/FVC 60; FEF 25-75% 0.83(37.4%); DLCO 19.43(81.9%)
- 8/5/2019: FVC 3.03(91%); FEV1 1.83(72%); FEV1/FVC 61; FEF 25-75% 0.78(36%); FEV1 improved to 2.19(19% change) which is consistent with +BD response; TLC 5.42(106%); RV 2.23(110%); DLCO 18.65(79%)
- 10/19/2020: FVC 2.78(90.5%), FEV1 1.79(74.9%), FEV1/FVC 64, FEF 25-75 0.87(43%), TLC 5.32(104%), DLCO 15.51(75%)
- 8/30/22: FVC 2.20 (80%); FEV1 1.48 (66%); FEV1/FVC 65; FEF 25-75% 0.80(42%); DLCO 17.44 (73%)

HRCT Chest Imaging (2016)





Current Patient Status

- 3 drug regimen for her precapillary PH (ERA; PDE5-I; inhaled treprostinil)
- Leflunomide 20mg daily; sulfasalazine 1000mg BID; plaquenil 200mg BID
- Chronic DOAC
- Uses 2 liters oxygen around the clock (lives at altitude about 6000 feet); limited with more than ordinary activity on exertion