

CHEST[®]

Official publication of the American College of Chest Physicians



The Many Faces of Merlin : IgG4-Associated Pulmonary-Renal Disease

Ben Sprangers, Pieter Lioen, Björn Meijers, Evelyne Lerut, Joke Meersschaert, Daniel Blockmans and Kathleen Claes

Chest 2011;140:791-794
DOI 10.1378/chest.10-3086

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
<http://chestjournal.chestpubs.org/content/140/3/791.full.html>

Chest is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2011 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(<http://chestjournal.chestpubs.org/site/misc/reprints.xhtml>)
ISSN:0012-3692



are similar to those in adult or reinfection TB, specifically progressive infiltrate in the upper lobe, cavitation, and signs of fibrosis.²³

In the case presented here, the history of exposure to bats suggested a fungal pulmonary disease, which was confirmed by the isolation of *H capsulatum* from a BAL sample culture. In conclusion, pulmonary histoplasmosis should be included in the spectrum of the diseases that may present with the RHS on HRCT scan.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

REFERENCES

- Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology*. 2008;246(3):697-722.
- Kim SJ, Lee KS, Ryu YH, et al. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. *AJR Am J Roentgenol*. 2003;180(5):1251-1254.
- Voloudaki AE, Bours DE, Froudarakis ME, Datsis GE, Apostolaki EG, Gourtsoyiannis NC. Crescentic and ring-shaped opacities. CT features in two cases of bronchiolitis obliterans organizing pneumonia (BOOP). *Acta Radiol*. 1996;37(6):889-892.
- Marchiori E, Grando RD, Simões Dos Santos CE, et al. Pulmonary tuberculosis associated with the reversed halo sign on high-resolution CT. *Br J Radiol*. 2010;83(987):e58-e60.
- Gasparetto EL, Escuissato DL, Davaus T, et al. Reversed halo sign in pulmonary paracoccidioidomycosis. *AJR Am J Roentgenol*. 2005;184(6):1932-1934.
- Wahba H, Truong MT, Lei X, Kontoyiannis DP, Marom EM. Reversed halo sign in invasive pulmonary fungal infections. *Clin Infect Dis*. 2008;46(11):1733-1737.
- Ahuja A, Gothi D, Joshi JM. A 15-year-old boy with "reversed halo." *Indian J Chest Dis Allied Sci*. 2007;49(2):99-101.
- Tzilas V, Bastas A, Provata A, Koti A, Tzouda V, Tsoukalas G. The "reversed halo" sign in pneumococcal pneumonia: a review with a case report. *Eur Rev Med Pharmacol Sci*. 2010;14(5):481-486.
- Chung JH, Godwin JD, Chien JW, Pipavath SJ. Case 160: pulmonary mucormycosis. *Radiology*. 2010;256(2):667-670.
- Otera H, Tada K, Sakurai T, Hashimoto K, Ikeda A. Reversed halo sign in pneumocystis pneumonia: a case report. *BMC Med Imaging*. 2010;10:26.
- Maimon N. A 47-year-old female with shortness of breath and "reversed halo sign". *Eur Respir Rev*. 2010;19(115):83-85.
- Bravo Soberón A, Torres Sánchez MI, García Río F, Sánchez Almaraz C, Parrón Pajares M, Pardo Rodríguez M. High-resolution computed tomography patterns of organizing pneumonia [in Spanish]. *Arch Bronconeumol*. 2006;42(8):413-416.
- Walsh SL, Robertson BJ. Images in thorax. The atoll sign. *Thorax*. 2010;65(11):1029-1030.
- Zompatori M, Poletti V, Battista G, et al. Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign). A case report. *Radiol Med*. 1999;97(4):308-310.
- Benamore RE, Weisbrod GL, Hwang DM, et al. Reversed halo sign in lymphomatoid granulomatosis. *Br J Radiol*. 2007;80(956):e162-e166.
- Agarwal R, Aggarwal AN, Gupta D. Another cause of reverse halo sign: Wegener's granulomatosis. *Br J Radiol*. 2007;80(958):849-850.
- Choi YH, Im JG, Park CK. Notes from the 2001 Annual Meeting of the Korean Society of Thoracic Radiology. *J Thorac Imaging*. 2002;17(2):170-175.
- Kanaji N, Bandoh S, Nagamura N, et al. Lipoid pneumonia showing multiple pulmonary nodules and reversed halo sign. *Respir Med Extra*. 2007;3(3):98-101.
- Kumazoe H, Matsunaga K, Nagata N, et al. "Reversed halo sign" of high-resolution computed tomography in pulmonary sarcoidosis. *J Thorac Imaging*. 2009;24(1):66-68.
- Marchiori E, Zanetti G, Mano CM, Hochegger B, Irion KL. The reversed halo sign: another atypical manifestation of sarcoidosis. *Korean J Radiol*. 2010;11(2):251-252.
- Marlow TJ, Krapiva PI, Schabel SI, Judson MA. The "fairly ring": a new radiographic finding in sarcoidosis. *Chest*. 1999;115(1):275-276.
- Tokuyasu H, Isowa N, Shimizu E, Yamadori I. Reversed halo sign associated with dermatomyositis. *Intern Med*. 2010;49(15):1677-1678.
- Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, et al. Cryptogenic and secondary organizing pneumonia: clinical presentation, radiographic findings, treatment response, and prognosis. *Chest*. 2011;139(4):893-900.
- Marchiori E, Zanetti G, Hochegger B, Irion KL. Re: reversed halo sign: nodular wall as criterion for differentiation between cryptogenic organizing pneumonia and active granulomatous diseases. *Clin Radiol*. 2010;65(9):770-771.
- Aidé MA. Chapter 4—histoplasmosis. *J Bras Pneumol*. 2009;35(11):1145-1151.
- Fraser RS, Müller NL, Colman N, et al. *Diagnosis of Diseases of the Chest*. 4th ed. Philadelphia, PA: WB Saunders; 1999.
- Zöllner MS, Rezende KM, Birman S, Elias CP, Arisawa EA, Santos MA. Clinical and evolutionary characteristics of four patients with pulmonary histoplasmosis reported in the Paraíba Paulista Valley region. *Rev Soc Bras Med Trop*. 2010;43(5):599-601.
- Leimann BC, Pizzini CV, Muniz MM, et al. Histoplasmosis in a Brazilian center: clinical forms and laboratory tests. *Rev Iberoam Micol*. 2005;22(3):141-146.
- Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev*. 2007;20(1):115-132.

The Many Faces of Merlin

IgG4-Associated Pulmonary-Renal Disease

Ben Sprangers, MD, PhD; Pieter Lioen, MD;
Björn Meijers, MD, PhD; Evelyn Lerut, MD, PhD;
Joke Meerschaert, MD; Daniel Blockmans, MD, PhD;
and Kathleen Claes, MD

Pulmonary-renal syndrome is a common and serious disorder with a broad differential diagnosis. We describe a case of a middle-aged man presenting with interstitial pulmonary disease and severe renal impairment caused by a hypocomplementemic immune-complex-mediated interstitial nephritis. Serum levels of IgG4 were elevated, and renal biopsy specimens revealed the presence of interstitial IgG4⁺ plasma cells. There was a rapid improvement of both

pulmonary and renal abnormalities after the initiation of corticosteroids. To our knowledge, this report is the first to show interstitial pulmonary disease in association with interstitial kidney disease as the predominant and presenting symptoms of IgG4-related disease. *CHEST 2011; 140(3):791–794*

Abbreviations: TIN = tubulointerstitial nephritis

CASE REPORT

A 57-year-old man of North African origin presented at the ED with a history of weight loss (8 kg in 3 months), anorexia, and lower back pain. Six months earlier, he had been hospitalized elsewhere for dyspnea and patchy pulmonary infiltrates. No diagnosis was made at that point, and no treatment was initiated. His previous medical history included obesity, benign prostate hypertrophy, and diabetes mellitus type 2. At the time of admission, his treatment consisted of terazosin and metformin. There was no history of nonsteroidal antiinflammatory drugs or illicit drug use.

On clinical examination, crepitations over the dorsobasal part of the right lung and arterial hypertension (147/92 mm Hg) were noted. Biochemical investigation showed a serum creatinine level of 5.79 mg/dL and a BUN level of 56 mg/dL. Isolated WBCs were detected by urine analysis. There were no RBCs detected in the urine, and mild proteinuria was present (0.6 g/24 h). A chest radiograph showed bilateral patchy infiltrates and evidence of interstitial pulmonary disease, which was confirmed on chest CT scans (Fig 1A). Thickening of the bronchovascular bundles was predominantly present in the perihilar regions in combination with thickened interlobular septa (Fig 1A).

On renal ultrasonography examination, enlarged kidneys with signs of acute parenchymal damage were seen. Based on the initial findings, the differential diagnosis included Goodpasture syndrome, systemic vasculitis, and pneumonia. Initial treatment consisted of IV antibiotics (ceftriaxone and clarithromycin) and crystalloid fluids.

Bronchoscopy with BAL (culture, cytology, polymerase chain reaction) and bronchial biopsy specimens did not reveal abnormalities. There was no evidence of infection following blood and sputum cultures and serologic screening. Autoimmune screening revealed antinuclear antibody positivity (1/160, negative Farr assay, negative extractable nuclear antigens, including Ro/SSA and La/SSB antibodies), and

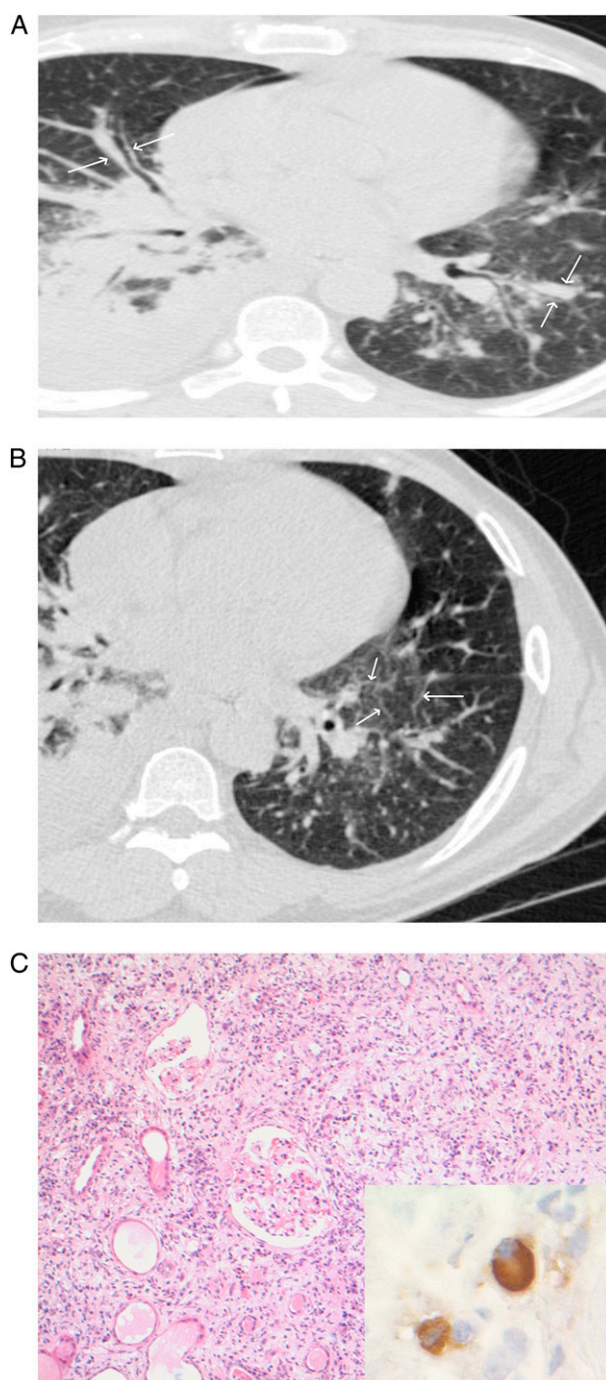


FIGURE 1. Radiographic and histologic findings at the time of presentation. A, B, High-resolution chest CT scans show multiple ill-defined consolidations mainly in the right lung associated with the presence of pleural effusion. Thickening of the bronchovascular bundles were seen predominantly in the perihilar regions (arrows, A) in combination with thickened interlobular septa (arrows, B). A right-sided pleural effusion also was present. C, Light microscopy of a kidney biopsy specimen, with hematoxylin-eosin stain (original magnification $\times 100$) showing tubulointerstitial nephritis as evidenced by an extensive lymphoplasmacytic infiltration and prominent atrophic tubules. Only a few eosinophils were present, and no granulomas were noted. The glomeruli present in the biopsy specimen showed no abnormalities. Immunohistochemical IgG4-staining (original magnification $\times 630$ [inset]) showed cytoplasmic IgG4 positivity of infiltrating plasma cells.

Manuscript received November 30, 2010; revision accepted January 19, 2011.

Affiliations: From the Department of Nephrology (Drs Sprangers, Meijers, and Claes), Department of General Internal Medicine (Drs Lioen and Blockmans), Department of Pathology (Dr Lerut), and Department of Radiology (Dr Meerschaert), University Hospitals Leuven, Leuven, Belgium.

Correspondence to: Kathleen Claes, MD, Department of Nephrology, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium; e-mail: kathleen.claes@uzleuven.be
© 2011 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (<http://www.chestpubs.org/site/misc/reprints.xhtml>).

DOI: 10.1378/chest.10-3086

low complement factors (C3, 0.60 g/L [normal range, 0.79-1.52 g/L]; C4, 0.03 g/L [normal range, 0.16-0.38 g/L]). Tests for antineutrophil cytoplasmic and antiglomerular basement membrane antibodies, rheumatic factor, and cryoglobulin level were negative. Kininase II was within normal levels, and no paraprotein was identified in urine or blood. A lip biopsy specimen and Schirmer test results were negative.

Because of severe acute kidney injury without improvement after fluid challenge, a renal biopsy was performed, and the specimen showed diffuse, nongranulomatous tubulointerstitial nephritis (TIN) (Fig 1C). Within the lymphoplasmocytic inflammatory infiltrate, there were large clusters of IgG4⁺ plasma cells (Fig 1C inset). Serum levels of IgG4 were markedly elevated (6.9 g/L; normal range, 0.08-1.4 g/L), and serum IgG levels were normal. The diagnosis of hypocomplementemic immune-complex-mediated TIN as a consequence of IgG4-related disease was made. Therapy with corticosteroids was initiated (3 days methylprednisolone 250 mg IV; thereafter, 48 mg po with taper). After the initiation of corticosteroids, a rapid partial recovery of renal function was seen (Fig 2A) as well as a gradual disappearance of pulmonary lesions on imaging. Further radiologic screening suggested chronic pancreatitis, prostatitis, and primary sclerosing cholangitis phase 3 (vanishing bile duct disease). After 2 months of steroid therapy, the patient's serum creatinine level declined to 2.16 mg/dL (estimated glomerular filtration rate, 30 mL/min/1.73 m²) with normalization of chest radiography and IgG4 and complement levels (Figs 2A, 2B).

DISCUSSION

The association of interstitial pulmonary disease with acute TIN is most often caused by sarcoidosis. In the latter, however, hypocomplementemia rarely is present, and interstitial granulomas usually are found. Hypocomplementemic immune-complex-mediated TIN is rare, especially in the absence of autoimmune disease, such as systemic lupus erythematosus or Sjögren syndrome.¹ Here, we diagnosed IgG4-related disease as the cause of TIN and interstitial lung disease. In recent years, IgG4-related disease has been reported as a cause of hypocomplementemic immune-complex-mediated TIN; moreover, pulmonary involvement has been increasingly recognized.² IgG4-related disease is a systemic disease characterized by multifocal fibrosclerosis and infiltration of IgG4⁺ plasmocytes that can affect the aorta, pancreas, lacrimal glands, lymph nodes, and lung and renal tissue.³⁻⁵ Elevated levels of serum IgG4 and infiltration of IgG4⁺ plasma cells are the hallmarks of this disease entity.

IgG4-related disease recently has been reported to be associated with pulmonary disease. Different pulmonary manifestations have been described, including interstitial lung disease, pulmonary inflammatory pseudotumor, lymphomatoid granulomatosis, bronchiolitis obliterans with organizing pneumonia, nonspecific interstitial pneumonia, and lymphoplasmacytic inflammation. Inoue et al⁶ proposed a classification of IgG4-related lung disease based on the predominant radiologic abnormality. The following four subtypes were identified: solid nodular type having a solitary nodular lesion; round-shaped, ground-glass opacity

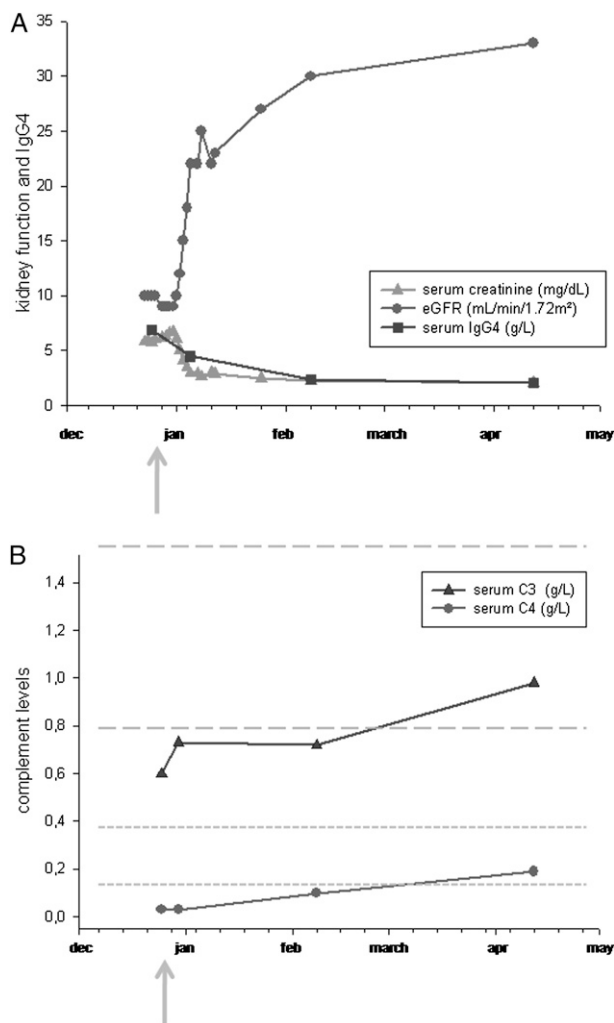


FIGURE 2. Evolution of renal function, IgG4, and complement with corticosteroid treatment. A, Evolution of serum creatinine (▲), eGFR (●), and IgG4 (■) serum levels from the time of presentation onward. The arrow indicates the start of corticosteroid treatment. B, Evolution of serum complement factors C3 (▲) and C4 (●) from the time of presentation onward. The arrow indicates the start of corticosteroid treatment. Dashed lines denote normal upper and lower limits of C3, and dotted lines denote normal upper and lower limits of C4. eGFR = estimated glomerular filtration rate.

type characterized by multiple round-shaped, ground-glass opacities; alveolar interstitial type showing honeycombing, bronchiectasis, and diffuse ground-glass opacities; and bronchovascular type showing thickening of bronchovascular bundles and interlobular septa. Applying this classification, the present case can be classified into the bronchovascular type of IgG4-related lung disease. Furthermore, Inoue et al⁶ showed that radiologic features are correlated with pathologic findings. The solitary nodular lesions consisted of diffuse infiltration of mononuclear cells (lymphocytes and plasma cells) in association with fibrosis. Lymphoplasmacytic infiltration and fibrosis in peribronchiolar or interlobular interstitium and alveolar interstitium correlated with thickened bronchovascular bundles or interlobular septa and ground-glass opacities on CT images, respectively. The radiologic findings of honeycombing corresponded to disrupted alveolar structures and dilated peripleural air spaces.

Presenting symptoms of IgG4-related disease vary substantially, raising questions about its precise pathogenesis and the role of IgG4. Moreover, whether IgG4-related disease represents a separate disease entity is a matter of controversy.⁴ IgG4 is the rarest IgG subclass, and elevated titers of IgG4 are found in pemphigus foliaceus, pemphigus vulgaris, bronchial asthma, and atopic dermatitis. Although IgG4-related disease is associated with hypocomplementemic immune-complex-mediated TIN, IgG4 itself is unable to fix and activate complement, and as such, IgG4 is believed to represent an antiinflammatory antibody. The identity of the target autoantigen in IgG4-related disease is unclear, although Aoki et al⁷ found IgG4 autoantibody reactivity directed toward the epithelium of pancreatic ducts, bile ducts, and salivary gland ducts. Hence, the demonstration of deposits of immune complexes along the tubular basement membrane suggests that the causative renal antigen might be localized at this site.

In summary, this report is the first, to our knowledge, of interstitial kidney disease in association with interstitial pulmonary disease as the predominant and presenting symptoms of IgG4-related disease. As indicated, the response to corticoid steroid therapy was favorable.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: This study was approved by the Institutional Review Board of the University Hospitals Leuven "Commissie Medische Ethiek van de Universitaire Ziekenhuizen KULeuven" ML6839. Informed consent was obtained from the patient.

REFERENCES

1. Vaseemuddin M, Schwartz MM, Dunea G, Kraus MA. Idiopathic hypocomplementemic immune-complex-mediated tubulointerstitial nephritis. *Nat Clin Pract Nephrol*. 2007;3(1):50-58.
2. Yamashita K, Haga H, Kobashi Y, Miyagawa-Hayashino A, Yoshizawa A, Manabe T. Lung involvement in IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis: report of 3 cases and review of the literature. *Am J Surg Pathol*. 2008;32(11):1620-1626.
3. Stone JH, Khosroshahi A, Hilgenberg A, Spooner A, Isselbacher EM, Stone JR. IgG4-related systemic disease and lymphoplasmacytic aortitis. *Arthritis Rheum*. 2009;60(10):3139-3145.
4. Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis*. 2009;68(8):1310-1315.
5. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol*. 2008;14(25):3948-3955.
6. Inoue D, Zen Y, Abo H, et al. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. *Radiology*. 2009;251(1):260-270.
7. Aoki S, Nakazawa T, Ohara H, et al. Immunohistochemical study of autoimmune pancreatitis using anti-IgG4 antibody and patients' sera. *Histopathology*. 2005;47(2):147-158.

The Many Faces of Merlin : IgG4-Associated Pulmonary-Renal Disease

Ben Sprangers, Pieter Lioen, Björn Meijers, Evelyne Lerut, Joke Meersschaert, Daniel Blockmans and Kathleen Claes

Chest 2011;140; 791-794

DOI 10.1378/chest.10-3086

This information is current as of September 12, 2011

Updated Information & Services

Updated Information and services can be found at:

<http://chestjournal.chestpubs.org/content/140/3/791.full.html>

References

This article cites 7 articles, 2 of which can be accessed free at:

<http://chestjournal.chestpubs.org/content/140/3/791.full.html#ref-list-1>

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://www.chestpubs.org/site/misc/reprints.xhtml>

Reprints

Information about ordering reprints can be found online:

<http://www.chestpubs.org/site/misc/reprints.xhtml>

Citation Alerts

Receive free e-mail alerts when new articles cite this article. To sign up, select the "Services" link to the right of the online article.

Images in PowerPoint format

Figures that appear in *CHEST* articles can be downloaded for teaching purposes in PowerPoint slide format. See any online figure for directions.

