Cryptogenic organising pneumonia or acute fibrinous and organising pneumonia?

To the Editors:

In a recent issue of the *European Respiratory Journal*, CHEE *et al*. [1] present a case that was diagnosed and treated as cryptogenic organising pneumonia. We have a few comments about this case.

First, histology is described as follows: ''…diffuse intra-alveolar exudate of granular, fibrinous material…''. Organising pneumonia pattern, the histological hallmark of cryptogenic organising pneumonia, is characterised by intra-alveolar buds of granulation tissue. Recently, a new anatomo-clinical entity has been reported by BEASLEY *et al*. [2] as ''acute fibrinous and organizing pneumonia (AFOP)''. The clinical spectrum of this entity may be similar to cryptogenic organising pneumonia and, taking into account the morphological features on surgical lung biopsy specimens, in our opinion, the case reported by CHEE *et al*. [1] is more consistent with this diagnostic hypothesis.

Secondly, the diagnostic approach described in the paper by CHEE *et al*. [1] is dissimilar to that usually followed in our centre (GB Morgagni Hospital, Azienda USL di Forlì, Forlì, Italy). In patients with alveolar opacification shadows, bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy may contribute to a definitive diagnosis in >60% of cases [3, 4], with fine-needle aspiration being less sensitive and specific [5].

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REFERENCES

1 Chee CBE, Da Costa JL, Sim CS. A female with dry cough, progressive dyspnoea and weight loss. *Eur Respir J* 2005; 25: 206–209.
2 Beasley MB, Franks TJ, Galvin JR, Gochuico B, Travis WD. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. *Arch Pathol Lab Med* 2002; 126: 1064–1070.
3 Dina R, Sheppard MN. The histological diagnosis of clinically documented cases of cryptogenic organising pneumonia. Diagnostic features in transbronchial biopsies. *Histopathology* 1993; 23: 541–545.
4 The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. Introduction. *Thorax* 1999; 54: Suppl. 1, 1–14.
5 Poletti V, Chilosi M, Olivieri D. Diagnostic invasive procedures in diffuse infiltrative lung diseases. *Respiration* 2004; 71: 107–119.

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From the author:

We thank V. Poletti and G.L. Casoni for their comments and interest in our case report [1].

Acute fibrinous and organising pneumonia is certainly a possible differential diagnosis in our patient. However, the patient's subacute presentation, dramatic response to steroids and clinical course were more in keeping with, and indeed typical of, cryptogenic organising pneumonia. In contrast, in the original series by BEASLEY *et al*. [2], of 17 patients with the histological diagnosis of acute fibrinous and organising pneumonia, nine patients had a fulminant course with rapid progression to death. Of the seven patients in this series who were treated with steroids (with or without antibiotics), only two survived. It should also be noted that the histological diagnosis of acute fibrinous and organising pneumonia was made from open lung and autopsy specimens in all cases.

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REFERENCES

1 Chee CBE, Da Costa JL, Sim CS. A female with dry cough, progressive dyspnoea and weight loss. *Eur Respir J* 2005; 25: 206–209.
2 Beasley MB, Franks TJ, Galvin JR, Gochuico B, Travis WD. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. *Arch Pathol Lab Med* 2002; 126: 1064–1070.

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The immune response to resistive breathing

To the Editors:

The excellent review by VASSILAKOPOULOS *et al*. [1] discusses in detail the immune response to resistive breathing. The authors report the systemic effects of resistive breathing (cytokines in plasma), as well as the effects of resistive loads on the respiratory muscles (diaphragm).

To the extent that resistive breathing is a potent stimulus for upregulation of cytokines involved in the process of angiogenesis, a review dealing with the immune response to resistive breathing may present the angiogenetic response as well.

Exercise training induces a series of adaptive responses in the cardiovascular and skeletal muscular system, including myofibrillar protein changes, increased activity of oxidative and glycolytic enzymes, and an increased number of capillaries. Such changes in the capillary bed of skeletal muscles in athletes have been detected since the mid 1970s [2, 3]. Since then, angiogenesis has been studied extensively and found to be an extremely complex process involving, among others, the dissolution of the extra cellular matrix underlying endothelium, cell migration and endothelial cell proliferation [4, 5]. Specific growth factors and predominantly vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and transforming growth factor (TGF)-b1 were found to regulate the angiogenic response to a variety of stimuli [4]. A single bout of exercise increases the mRNA levels for the previously mentioned factors [6]. Recent data have shown that acute exercise upregulates the mRNA expression, while there is a graded response in the expression of mRNA of this angiogenic factor with the metabolic stress. Furthermore, it is demonstrated that mRNA for VEGF and bFGF in the diaphragm of rats rises significantly as a result of active increased ventilation due to hypoxia and/or hypercapnia, while no changes in mRNA levels were observed in paralysed, mechanically ventilated animals at similar arterial blood gases and ventilation levels [7, 8]. However, there is evidence that resistive breathing upregulates mRNA for VEGF, but not for bFGF and TGF-b1 [9].

Therefore, angiogenesis, as a result of loading of the respiratory system, is an important part of the integrated immune response to resistive breathing.

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REFERENCES

1 Vassilakopoulos T, Roussos C, Zakynthinos S. The immune response to resistive breathing. *Eur Respir J* 2004; 24: 1033–1043.
2 Andersen P, Henriksson J. Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. *J Physiol* 1977; 270: 677–690.
3 Andersen P, Henriksson J. Training induced changes in the subgroups of human type II skeletal muscle fibres. *Acta Physiol Scand* 1977; 99: 123–125.
4 Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. *Physiol Rev* 1992; 72: 369–417.
5 Booth FW, Thomason DB. Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. *Physiol Rev* 1991; 71: 541–585.
6 Breen EC, Johnson EC, Wagner H, Tseng HM, Sung LA, Wagner PD. Angiogenic growth factor mRNA responses in muscle to a single bout of exercise. *J Appl Physiol* 1996; 81: 355–361.
7 Roca J, Gavin TP, Jordan M, *et al.* Angiogenic growth factor mRNA responses to passive and contraction-induced hyperperfusion in skeletal muscle. *J Appl Physiol* 1998; 85: 1142–1149.
8 Siafakas NM, Jordan M, Wagner N, Breen EC, Benoit H, Wagner PD. Diaphragmatic angiogenic growth factor mRNA responses to increased ventilation caused by hypoxia and hypercapnia. *Eur Respir J* 2001; 17: 681–687.
9 Jordan MWH, Breen EC, Benoit H, Wagner PD, Siafakas NM. Effect of resistive loading on angiogenic growth factor mRNA of the respiratory muscles. *Am J Respir Crit Care Med* 1998; 157: A669.

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From the authors:

We would like to thank N.M. Siafakas and I. Mitrouska for their insightful comments about our recent article published in the *European Respiratory Journal* [1]. They suggest that resistive breathing may be a potent stimulus for upregulation of angiogenesis-promoting factors within the diaphragm.

Preliminary data (which have appeared only in abstract form) suggest that resistive breathing might lead to an upregulation of vascular endothelial growth factor (VEGF), but not basic fibroblast growth factor (bFGF) and transforming growth factor-b1 [2]. Other forms of increased diaphragmatic activation, such as hyperventilation induced by hypercapnia and/or hypoxia, lead to increased expression of the mRNA levels of both VEGF and bFGF [3]. This angiogenetic response was not solely caused by the deranged blood gases or by the hyperventilation-induced passive stretching and shortening of the diaphragm, since mechanical ventilation leading to similar blood gases levels did not result in a diaphragmatic angiogenetic response.

The stimuli for the expression of angiogenesis-promoting factors within skeletal muscles (in general) and respiratory muscles (in particular) remain elusive. Interestingly, in an *in vitro* cell culture system of skeletal myocytes fused into myotubes, reactive oxygen species stimulated the expression of VEGF [4] in a similar fashion to their effect of inducing interleukin-6 production [5]. This raises the interesting possibility that oxidative stress generated intramuscularly, secondary to increased muscular activation/contraction [6], might be the stimulus for both upregulation of cytokines and expression of an angiogenesis programme. Despite being sound, such a hypothesis has never been experimentally tested.

Angiogenesis is a prerequisite for the development of hypertrophy and hyperplasia, secondary to chronic exercise training in skeletal muscles. This might be important for the increased ventilation requirements of some elite athletes during athletic performance, although the benefit from additional specific respiratory muscle training is uncertain [7]. However, angiogenesis is even more important for the beneficial effects of rehabilitation programmes involving training of the respiratory muscles [8].

Our review focused on the response of the ''classical'' cytokines (those usually produced by blood mononuclear cells) to resistive breathing. This is why it did not cover other