Elevated N-terminal pro-brain natriuretic peptide in *Mycobacterium tuberculosis* pulmonary infection without myocardial dysfunction

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Increased levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) in infectious settings may not reflect myocardial depression. In addition to NT pro-BNP measurement, clinical assessment remains a valuable tool for diagnosis and prognosis of heart failure. A case of excessively increased NT pro-BNP level associated with *Mycobacterium tuberculosis* infection that was not indicative of myocardial dysfunction is described.

Key Words: Congestive heart failure; *Mycobacterium tuberculosis*; Natriuretic peptides

Reports of elevated N-terminal pro-brain natriuretic peptide (NT pro-BNP) in nonheart failure settings have started to become more frequent in the literature (1-4). We and others (4) have reported increased NT pro-BNP levels in critical illnesses and sepsis, apparently independent of myocardial dysfunction. Heart failure is a chronic medical condition, with a poor prognosis comparable with that of cancer (5). Brain natriuretic peptide (BNP) is considered to be the gold standard biomarker for cardiac dysfunction (6), and most data in literature associate its increased levels with myocardial dysfunction (3,7-9).

In human myocardium, BNP is secreted in response to myocardial stretch. Its release promotes natriuresis and diuresis, and has a vasodilatory effect on systemic circulation (10). As such, it reduces preload, venous return and filling pressures with a subsequent reduction in cardiac output (11). Its value changes with increased left ventricular (LV) end-diastolic pressure, pulmonary artery wedge pressure, atrial pressure and LV hypertrophy (12). Impaired cardiac function correlates to the magnitude of increase in BNP level (13). In addition to the documented relationship between BNP and myocardial dysfunction mentioned above, other conditions associated with increased BNP level include primary pulmonary hypertension, myocarditis, cardiac allograft rejection, arrhythmogenic right ventricle with decreased LV ejection fraction, renal failure, Kawasaki disease, ascitic cirrhosis and endocrine diseases (Cushing's syndrome, primary hyperaldosteronism) (12). Independent parameters that may influence the BNP level include advancing age, probably reflecting LV subclinical abnormalities (13), and female sex, both of which result in increased BNP levels (14,15). In contrast, obesity is associated with decreased levels of BNP, probably as a result of increased clearance through a receptor contained in adipose tissue (16).

Tuberculosis is a systemic disease associated with a compromised immune system (17); it is the number one infectious disease killer worldwide (18,19), which continues to grow despite energetic attempts to control it after more than a century of study (20,21).

Un taux élevé de peptide natriurétique N-terminal de type B non relié au dysfonctionnement myocardique : Une infection à *Myocabacterium tuberculosis*

Des taux élevés de peptide natriurétique N-terminal de type B (NT pro-BNP) dans un contexte infectieux ne reflètent pas nécessairement une dépression myocardique. En plus de la mesure du NT pro-BNP, l'évaluation clinique demeure un outil précieux pour le diagnostic et le pronostic d'insuffisance cardiaque. Les auteurs décrivent un cas de taux beaucoup trop élevé de NT pro-BNP associé à une infection à *Myocabacterium tuberculosis* non indicatrice de dysfonctionnement myocardique.

Humans are the only known reservoir for *Mycobacterium tuberculosis* (22), and its potential to produce a septic state is well known (23,24). The impact of tuberculosis on the human species has been demonstrated in mummies up to 2000 years old (25). On entering the new host, bacilli inside the macrophages may be killed by the immune system, which happens in approximately 90% of cases. Multiplication with subsequent progressive primary tuberculosis happens in approximately 5% of cases. In the remaining 5% of cases, bacilli may become dormant and remain asymptomatic, or they may proliferate after a latency period (26,27). *M tuberculosis* cells produce approximately eightfold more nitrite than those of aerobic cultures the same age (28), a characteristic that contributes to persistence of *M tuberculosis* in tissues.

We present a case of infection with *M tuberculosis* with markedly elevated levels of NT pro-BNP and no evidence of myocardial dysfunction based on clinical evaluation and catheterization. To our knowledge, this is the first reported case of excessively elevated NT pro-BNP in conjunction with *M tuberculosis*. Also described are possible explanations of elevated NT pro-BNP in this setting. Consequently, we emphasize the need for a careful clinical evaluation in correlation with laboratory investigations in infectious settings with excessively elevated NT pro-BNP values.

CASE PRESENTATION

A 56-year-old man with a history of diabetes, chronic renal impairment and paroxysmal atrial fibrillation underwent heart transplantation in 1999 for end-stage heart failure secondary to chemotherapy for non-Hodgkin's lymphoma. He presented to his family doctor with a one-month history of cough, shortness of breath, fever, headache and weight loss of approximately 9 kg over two months. His cough was productive of white sputum, and he was treated empirically for respiratory infection with ciprofloxacin. Subsequently, he was admitted to the community hospital. Because the patient's condition continued to deteriorate, he was transferred to St Paul's Hospital (Vancouver,

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Figure 1) Initial chest x-ray showing bilateral interstitial infiltrates

British Columbia) in June 2006 with an increasing fever over 48 h to 72 h up to 39°C, progressive anemia and increasing creatinine up to 320 µmol/L (normal value 60 µmol/L to 100 µmol/L) (baseline 110 µmol/L). His temperature on admission was 38.9°C, his blood pressure was 110/65 mmHg, his heart rate was 126 beats/min and his oxygen saturation was 95% on 4 L nasal prongs and 89% on room air. An objective examination revealed a middle-aged man in no apparent distress, with crackles at the lung bases, jugular venous pulsations of 3 cm to 4 cm above the sternal angle and no peripheral edema. His abdomen was soft and mildly tender in the right upper quadrant, with no rebound and no organomegaly. There was no skin rash, and he denied joint pain. Investigations showed an initial white blood count of $5.2 \times 10^9/L$ (normal value $4 \times 10^9/L$ to $11 \times 10^9/L$), hemoglobin of 80 g/L (normal value 131 g/L to 169 g/L) and creatinine of 159 µmol/L. On admission, his NT pro-BNP was markedly elevated at 32,611 pg/mL (normal value lower than 855 pg/mL), suggesting severe heart failure. A chest x-ray showed bilateral interstitial infiltrates (Figure 1), and a computed tomography lung scan showed ground glass appearance on the right side. Treatment with steroids was immediately initiated in view of a possible graft rejection or accelerated graft vasculopathy, and the patient was sent urgently for a heart catheterization. Right heart catheterization showed a cardiac index of 3.3 L/min, LV end-diastolic pressure of 17 mmHg and pulmonary artery wedge pressure of 22 mmHg. An LV angiogram showed an ejection fraction of 65% and no wall motion abnormalities. The initial electrocardiogram is presented in Figure 2. Normal coronary arteries were documented angiographically, and a right heart biopsy performed at the same time showed no rejection. Antibiotic treatment was initiated with cefotaxime and azithromycin to cover typical and atypical community-acquired pneumonia and trimethoprim-sulfamethoxazole for possible *Pneumocystis jiroveci* pneumonia. Bronchial brushing demonstrated benign desquamated bronchial epithelial cells and histiocytes, and it was negative for cancer cells; no opportunistic agent infection or viral inclusion was identified. A bronchoscopic examination provided a sample that was negative for *P jiroveci* pneumonia and positive for acid-fast bacilli. Blood cultures continued to be negative. An abdominal ultrasound examination was normal, and antimicrobial therapy was reconsidered. Azithromycin 500 mg four times daily and etambutol 2 g four times daily were initiated, with subsequent normalization of the computed tomography scan and an improved NT pro-BNP value of 8035 pg/mL two weeks later.

Figure 2) Initial electrocardiogram showing sinus tachycardia with premature ventricular complexes

DISCUSSION

We describe a patient infected with *M tuberculosis* who presented with elevated levels of NT pro-BNP and no documented evidence of heart failure on complementary investigations. Even though BNP has been considered to be an optimal marker for cardiac dysfunction, the lack of data to provide a rationale for its changes in non-cardiac-related situations suggests that the clinical assessment should be emphasized when evaluating patients with presumed myocardial depression.

Clinical evidence shows that *M tuberculosis* can persist in tissues for months to decades in an inactive state, yet with the ability to resume growth and trigger disease (20,26,29). Hypoxia is considered to be a major factor in maintaining this nonreplicating state (27,29). The nitrate reduction triggered by hypoxia may serve as a respiratory function in supporting the transformation of *M tuberculosis* from aerobic growth to a nonreplicating persistence and help bacilli survive in oxygen-depleted regions of inflammatory or necrotic tissue (30). Cytokine expression in tuberculosis correlates with cell type. Thus, granulomas, epithelioid cells and multinucleated giant cells have their own cytokine expression (31). Active pulmonary tuberculosis and subsequent alveolar inflammation result in the release of tumour necrosis factor- α (TNF- α) and interleukin-1 beta identified in bronchoalveolar fluid (32). Maximal concentration of TNF- α can be detected as early as two days after infection (33). Cytokine production correlates with clinical parameters (pulmonary involvement, body weight loss and fever) and disease status, and involves a concomitant release of the inhibitors at the local inflammatory sites (32). Cytokine release, particularly interleukin-1 beta and TNF- α from alveolar macrophages, is important in the host's defense against mycobacterial infection (17). Kuo et al (34) found that in patients with tuberculosis, nitric oxide amplifies synthesis of proinflammatory cytokines in alveolar macrophages.

It has been demonstrated that these proinflammatory cytokines upregulate BNP gene expression and secretion (35). One of the mechanisms by which BNP exerts its vasodilator effect is nitric oxide production (36). Increased nitric oxide production can have both beneficial and deleterious effects (37). Beneficial effects manifest by vasodilation in systemic and pulmonary territories and an increase in myocardial oxygen supply, as well as a preservation of the cardiac index. The deleterious effects manifest as a decrease in blood pressure and systemic vascular resistance, concomitant with poorer tissue oxygenation (37).

Therefore, a possible explanation for increased NT pro-BNP in our patient relates to the extent of cytokine production and subsequent stimulation of nitric oxide. Nitric oxide has the ability to autoregulate its own production (38) and, by negative feedback, to counteract the excessive cytokine release. The continued presence of TNF- α has a growth-promoting effect on *M tuberculosis* (39). Hence, the negative stimulation by means of nitric oxide is necessary to decrease the proinflammatory state and, consequently, the amount of TNF- α . Changes in our patient's clinical status, reflected in the resolution of the computed tomography changes and a decrease in NT pro-BNP level after initiation of antimicrobial treatment, suggest that the acute proinflammatory state was transient and part of a complex and persistent immune response of various degrees characteristic of *M tuberculosis*.

There are limitations to our study in terms of the measurement of cytokine production. In addition, our patient presented with renal

failure, a condition known to modify the NT pro-BNP level through decreased clearance or associated subclinical structural heart disease (14). Although *M tuberculosis* can increase the pulmonary pressure to a moderate degree with a subsequent increase in NT pro-BNP (40,41), the magnitude of the increase would not be as high as in our patient.

REFERENCES

- Chua G, Kang-Hoe L. Marked elevations in N-terminal brain natriuretic peptide levels in septic shock. *Crit Care* 2004;8:R248-50.
- Witthaut R, Busch C, Fraunberger P, et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: Impact of interleukin-6 and sepsis-associated left ventricular dysfunction. *Intensive Care Med* 2003;29:1696-702.
- Charpentier J, Luyt C, Fulla Y, et al. Brain natriuretic peptide: A marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 2004;32:660-5.
- Bar SL, Swiggum E, Straatman L, Ignaszewski A. Non-heart failure-associated elevation of amino terminal pro-brain natriuretic peptide in the setting of sepsis. *Can J Cardiol* 2006;22:263-6.
- Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* 2001;3:315-22.
- Gardner RS, Özalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;24:1735-43.
- De Groot P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak exercise oxygen consumption provide independent information for risk stratification in patients with stable congestive heart failure. *J Am Coll Cardiol* 2004;43:1584.
- Harrison A, Morrison IK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med* 2002;39:131-8.
- Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, von Scheidt W. Role of brain natriuretic peptide in risk stratification of patient with congestive heart failure. *J Am Coll Cardiol* 2001;38:1934.
- Valli N, Gobinet A, Bordenave L. Review of ten years of the clinical use of brain natriuretic peptide in cardiology. *J Lab Clin Med* 1999;134:437-44.
- Woods RL. Cardioprotective functions of atrial natriuretic peptide and B-type natriuretic peptide: A brief review. *Clin Exp Pharmacol Physiol* 2004;31:791-4.
- Peacock FW. The B-type natriuretic peptide assay: A rapid test for heart failure. *Cleve Clin J Med* 2002;69:243-51.
- Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: Effect of stretching. *Endocrinology* 1993;132:1961-70.
- Baggish AL, Cameron R, Anwaruddin S, et al. A clinical and biochemical critical pathway for the evaluation of patients with suspected acute congestive heart failure: The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) algorithm. *Crit Pathw Cardiol* 2004;3:171-6.
- Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: Impact of age and gender. *J Am Coll Cardiol* 2002;40:976.
- Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol* 2004;43:1590.
- Tobin MJ. Tuberculosis, lung infections, and interstitial lung disease in AJRCCM 2000. *Am J Respir Crit Care Med* 2001;164:1774-88.
- Iseman MD. Tuberculosis – still the #1 killer in infectious diseases. *Int J Clin Pract Suppl* 2000:78.
- Hlawatsch A, Kauczor HU, Thelen M. [Pulmonary tuberculosis – the current radiological diagnosis of an old disease.] *Radiologe* 2000;40:507-17.
- Collins FM. The immune response to mycobacterial infection: Development of new vaccines. *Vet Microbiol* 1994;40:95-110.
- James J. [The discovery of the tubercle bacillus by Robert Koch: A milestone for 123 years.] *Ned Tijdschr Geneesk* 2005;149:2921-6.
- Vincent V, Marchal G. *Mycobacterium tuberculosis* and its host. *Rev Prat* 2002;52:2111-4.
- Michel P, Barbier C, Loubiere Y, Hayon JH, Ricome JL. Three cases of septic shock due to tuberculosis without HIV pathology. *Intensive Care Med* 2002;28:1827-8.
- George S, Papa L, Sheils L, Magnussen CR. Septic shock due to disseminated tuberculosis. *Clin Infect Dis* 1996;22:188-9.
- Gomez I Prat J, De Souza SM. Prehistoric tuberculosis in America: Adding comments to a literature review. *Mem Inst Oswaldo Cruz* 2003;98(Suppl 1):151-9.
- Tufariello JM, Chan J, Flynn JL. Latent tuberculosis: Mechanisms of host and bacillus that contribute to persistent infection. *Lancet Infect Dis* 2003;3:578-90.
- Rivas-Santiago B, Vieyra-Reyes P, Araujo Z. Cell immunity response in human pulmonary tuberculosis. Review. *Invest Clin* 2005;46:391-412.
- Sohaskey CD, Wayne LG. Role of narK2X and narGHJI in hypoxic upregulation of nitrate reduction by *Mycobacterium tuberculosis*. *J Bacteriol* 2003;185:7247-56.
- Wayne LG, Sohaskey CD. Nonreplicating persistence of *Mycobacterium tuberculosis*. *Annu Rev Microbiol* 2001;55:139-63.
- Wayne LG, Hayes LG. Nitrate reduction as a marker for hypoxic shift-down of *Mycobacterium tuberculosis*. *Tuber Lung Dis* 1998;79:127-32.
- Mustafa T, Mogga SJ, Mfinanga SG, Morkve O, Sviland L. Immunohistochemical analysis of cytokines and apoptosis in tuberculous lymphadenitis. *Immunology* 2006;117:454-62.
- Tsao TCY, Li L, Hsieh M, Liao S, Chang KSS. Soluble TNF- α receptor and IL-1 receptor antagonist elevation in BAL in active pulmonary TB. *Eur Respir J* 1999;14:490-5.
- Theus SA, Cave MD, Eisenach KD. Intracellular macrophage growth rates and cytokine profiles of *Mycobacterium tuberculosis* strains with different transmission dynamics. *J Infect Dis* 2005;191:453-60.
- Kuo HP, Wang CH, Huang KS, et al. Nitric oxide modulates interleukin-1 β and tumor necrosis factor- α synthesis by alveolar macrophages in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2000;161:192-9.
- Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol* 2004;36:505-13.
- Van der Zander K, Houben AJ, Kroon AA, De Mey JG, Smits PA, de Leeuw PW. Nitric oxide and potassium channels are involved in brain natriuretic peptide induced vasodilatation in man. *J Hypertens* 2002;20:493-9.
- Vincent JL, Zhang H, Szabo C, Preiser JC. Effects of nitric oxide in septic shock. *Am J Respir Crit Care Med* 2000;161:1781-5.
- Ravichandran LV, Johns RA, Rengasamy A. Direct and reversible inhibition of endothelial nitric oxide synthase by nitric oxide. *Am J Physiol* 1995;268:H2216-23.
- Byrd TF. Tumor necrosis factor alpha (TNF α) promotes growth of virulent *Mycobacterium tuberculosis* in human monocytes iron-mediated growth suppression is correlated with decreased release of TNF α from iron-treated infected monocytes. *J Clin Invest* 1997;99:2518-29.
- Leuchte HH, Holzapfel M, Baumgartner RA, Neurohr C, Vogeser M, Behr J. Characterization of brain natriuretic peptide in long-term follow-up of pulmonary arterial hypertension. *Chest* 2005;128:2368-74.
- Fijalkowska A, Kurzyńska M, Torbicki A, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest* 2006;129:1313-21.