



# Locked-in Syndrome and Blue Toe Syndrome Caused by Cardiopulmonary Bypass

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Received 27 December 2008; Accepted 25 April 2009

## Abstract

Severe inflammation after cardiopulmonary bypass with the vasculitis of the acral extremity and vertebro-basilar arterial system leads to the locked-in syndrome and blue toe syndrome. In broad terms, systemic, idiopathic, and environmental factors provoke syndromes that present with digital discoloration or the blue toe syndrome. Painful digital discoloration, accompanied by ulceration, suggests vasculitis, involving small blood vessels. Definitive diagnosis usually requires histological documentation because vasculitic syndromes have no pathognomonic clinical features or laboratory test results.

The case introduced herein is that of a woman who developed the locked-in syndrome in conjunction with quadriplegia, loss of facial movement, speech loss, and loss of horizontal eye movements. She had initially presented with severe mitral stenosis and left atrial clot and undergone mitral valve replacement and clot extraction. The patient expired from multiple organ failure despite prolonged ventilatory support, including tracheotomy, and meticulous nursing care and antibiotic prophylaxis. Given the previously reported partial recovery from this syndrome with the use of steroids, we would advocate the use of such pharmacological agents.

*J Teh Univ Heart Ctr 3 (2010) 150-152*

**Keywords:** Cardiopulmonary bypass • Postoperative complications • Cardiac surgical procedures • Blue toe syndrome

## Introduction

The systemic inflammatory response to cardiopulmonary bypass is a modification of the physiological response to tissue injury or infection. Activation of leukocytes, platelets, complement, and factor XII by contact with the bypass circuit and surgical trauma is followed by the systemic secretion of cytokines and other inflammatory mediators. The induced expression of adhesion molecules on activated leukocytes and endothelial cells can result in the sequestration of white cells within tissues and a clinical syndrome, the systemic inflammatory response syndrome (SIRS), which differs quite widely among patients. In its extreme form, it can lead to multiple organ failure that often includes the adult respiratory distress syndrome, a condition associated

with massive leukocyte infiltration in the lung and high mortality.<sup>1</sup> The locked-in syndrome is a rare clinical entity consisting of quadriplegia, paralysis of the lower cranial nerve, mutism, and bilateral paresis of horizontal gaze and is associated with unaltered consciousness, with intact vertical eye movements and blinking allowing some form of human communication by way of eye codes. Furthermore, there is usually cranial nerve weakness with the sparing of only the more laterally placed nuclei.<sup>2</sup> The locked-in syndrome results most commonly from a lesion in vertical pons, although extensive bilateral destruction of cortical-bulbar and cortico-spinal tracts in the pedunculi cerebri may be responsible. Sensory impairment due to medial lemniscuses involvement and damage to the decussating fibers from the spinal tract of trigeminal nerve are inevitable. The lesion at

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the basis pontis spares the pathways for somatic sensation and the non-specific ascending system of neurons and fibers responsible for arousal and wakefulness; nevertheless, it interrupts the cortico-bulbar and cortico-spinal pathways, depriving the patient of speech and the ability to respond in any other way. The locked-in syndrome has been reported after ventral pontine infarction following basilar artery occlusion, air embolism,<sup>3, 4</sup> pontine hemorrhage,<sup>5</sup> tumor, trauma, heroin abuse, encephalitis,<sup>6</sup> hypoglycemia,<sup>7</sup> and Basilar artery ectasia.<sup>8</sup> We add here a new cause, which is severe inflammatory reaction due to cardiopulmonary bypass with the gangrene of the distal extremity or the blue toe syndrome.

## Case Report

A 45-year-old woman was admitted to our heart center with severe mitral stenosis and left atrial clot. The patient gave a history of shortness of breath on minimal exertion for one week and no cerebral symptoms, including headache, dizziness, transient ischemic attacks, or strokes. She was found to be fully conscious, alert, and oriented with stable vital signs. Blood pressure was 110/80 mmHg, and diastolic murmur was audible over the mitral area. Physical examination revealed intact cranial nerves, motor power, and sensation. There was no evidence of vasculitis such as Osler's nodes, Jane way pad, palmer erythema, or cyanosis of fingers. Blood investigation showed an erythrocyte sedimentation rate (ESR) of 4 mm with no leukocytosis and a white blood cell (WBC) of 10.000 mm<sup>3</sup>. The electrolytes and kidney and liver function were within normal limits. Chest X-ray showed prominence of the left cardiac border due to left atrial enlargement. Electrocardiography was indicative of no change, but two-dimensional echocardiography revealed a large bulky non-mobile thrombosis in the left atrium with severe mitral stenosis. The mitral valve area was 0.6 cm<sup>2</sup>, and the other cardiac valves were normal. Pre- and postoperative laboratory measurements included negative antinuclear antibodies and rheumatoid factor, and elevation of C4 & C3 components of complement; in addition, HBS Antigen (especially in polyarteritis nodosa) was negative.

The patient underwent open heart surgery via the ascending aorta and bicaval cannulation. The aorta was cross-clamped, and the heart was arrested with cold cardioplegia by achieving systemic hypothermia at 30 °C on the cardiopulmonary bypass. Intraoperatively, the stenotic mitral valve was found to have a bulky clot attached to the valve and wall of the left atrium. The diseased mitral valve and the clot were excised, and the left atrial cavity was irrigated with copious amounts of normal saline and a valve was thereafter implanted. The left ventricle was then filled completely with saline and blood and fully deaired. The patient was weaned successfully off cardiopulmonary bypass with inotropic support and

transferred to the intensive care unit. After 6 hours, blood pressure dropped and central venous pressure elevated and the extremity became cool and cyanotic. Inotropic support was commenced with dobutamine and adrenaline (2 and 1 mic/kg/min, respectively). On the third postoperative day, the inotropic drugs were tapered and blood pressure stabilized. By this point, however, the cyanosis had changed to gangrene and on the 12<sup>th</sup> postoperative day the acral part of the extremity was amputated and the specimen was sent for histopathological examination. In the histopathological examination, there was only non-specific vasculitis with thrombosis. The patient did not regain full consciousness on the following morning and was found to be quadriplegic with non-voluntary movements of the four limbs and face. The eyes could move only on the vertical plane, with both pupils having become small and fixed. After 72 hours, she managed to respond to questions only by blinking or moving her eyes vertically. Brain MRI revealed multiple infarction of the brainstem. Prolonged ventilatory support was maintained and eventually a tracheostomy was performed to facilitate tracheobronchial suctioning and weaning. Acute renal failure with anemia was managed and the kidneys recovered completely. However, the patient remained in this locked-in state for 4 weeks with no neurological improvement despite all ventilatory, nutritional, and nursing support. She eventually expired from hepatic failure and generalized sepsis.

## Discussion

During cardiopulmonary bypass, the interaction of blood with non-biological surfaces results in a whole-body inflammatory response which may increase the morbidity and lead to multiple organ dysfunction.<sup>9</sup> Be that as it may, brainstem involvement as the locked-in syndrome and gangrene of the acral part of the extremity as the blue toe syndrome is exceedingly rare. The locked-in syndrome was coined by Plum<sup>10</sup> to denote the state of quadriplegia and mutism with preserved consciousness demonstrated by communication via intact vertical eye movements. It is considered to be devastating sequels of an occlusion of the main basilar artery<sup>11</sup> or its para median branch causing pontine infarction as the occlusion of the basilar artery can rarely be compensated by collateral artery.<sup>12</sup> Infarction of the brain stem evokes a variety of syndromes, including the locked-in syndrome, in which the lesion spares the pathways for somatic sensation and the non-specific ascending system of neurons and fibers responsible for arousal and wakefulness but interrupts the cortico-bulbar and cortico-spinal pathways, depriving the patient of motor power, speech, and capacity. The locked-in syndrome has never been reported earlier due to post cardiopulmonary bypass inflammatory reaction. Partial or full recovery has been reported in patients with

the locked-in syndrome<sup>13</sup> and pharmacological treatment includes fibrinolytic therapy and anticoagulation for the prevention of thrombosis. Steroids can be helpful by decreasing the intracranial pressure.

A number of acquired conditions can cause the uncontrolled activation of the coagulation system. The most common is the anticardiolipin antibody syndrome, which is sometimes but not always associated with lupus-rheumatoid arthritis, scleroderma, or Sjogren's syndrome. These patients may have a false-positive syphilis test and elevated partial thromboplastin time (PTT). Diagnoses in the third category are often considered after a source of proximal emboli and a coagulation work-up having failed to suggest a cause of blue or purple toe. Painful digital discoloration accompanied by ulceration suggests vasculitis, involving blood vessels. Definitive diagnosis usually requires histological documentation because vasculitic syndromes have no pathognomonic clinical features or lab test results.

We here in add a new case, which is severe inflammatory reaction begotten by cardiopulmonary bypass. MRI can show abnormally single or multiple intensity regions, and prophylactic treatment with an H2 receptor antagonist is recommended to prevent the development of a stress ulcer in such patients. Prolonged ventilatory support, tracheostomy, respiratory physiotherapy, intensive nursing care, appropriate antibiotic prophylactic treatment, and adequate nutritional support for hepatic failure and management of acute renal failure are essential. The blue toe syndrome resulting from generalized cardiopulmonary bypass inflammation is extremely rare and has not been reported so far. We sought to treat our patient with vasodilator drugs and amputation of toe. Hepatic failure presenting as functional obstruction of the biliary tract is normally managed with a low fatty diet and nutritional support and stool softener. The diagnosis of the syndrome depends mainly on the clinical picture and demonstration of brain stem infarction.<sup>14</sup> The prognosis for life is usually poor; however, there have been reports of survival and recovery from the locked-in syndrome following pontine infarction.<sup>15</sup>

## Conclusion

The blue toe syndrome is devastating sequelae of post cardiopulmonary bypass strong inflammatory response. Neither the use of heparin-coated circuits nor the administration of a high-dose regimen of steroids or aprotinin prevented or attenuated the inflammatory response in our patient. Because multiple avenues are present to elicit the post cardiopulmonary bypass inflammatory response, further research seems necessary to determine the best strategy for its prevention.

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