

## CASE REPORTS

# Paraneoplastic pemphigus vulgaris resulted in takotsubo cardiomyopathy: A case report

Moustafa Elsheshtawy, Abdel Abdel-Shafy, Steven Siegel

Department of Medicine, Coney Island Hospital, Brooklyn, NY, USA

**Correspondence:** Moustafa Elsheshtawy. Address: Department of Medicine, Coney Island Hospital, 2601 Ocean Parkway, Room 4N98, Brooklyn, NY 11235, USA. Email: melsheshtawymd@gmail.com, moustafa.elsheshtawy@nychhc.org

**Received:** July 29, 2015

**Accepted:** August 11, 2015

**Online Published:** August 13, 2015

**DOI:** 10.5430/crim.v2n3p84

**URL:** <http://dx.doi.org/10.5430/crim.v2n3p84>

## Abstract

Paraneoplastic pemphigus (PNP) is an autoimmune bullous disease characterized by intractable stomatitis and is associated with different malignancies. Mortality, if associated with the disease, is usually attributed to skin lesion infection or respiratory failure. Reversible cardiomyopathy, also known as takotsubo cardiomyopathy, is a reversible left ventricular dysfunction that is always triggered by intense physical or emotional stressors. To our knowledge, this is the first case to report mortality in paraneoplastic pemphigus vulgaris from takotsubo cardiomyopathy. This case illustrates the psychosocial impact of serious skin diseases that can affect mortality even when there is a favorable prognosis.

## Keywords

Paraneoplastic pemphigus, B cell lymphoma, Takotsubo cardiomyopathy

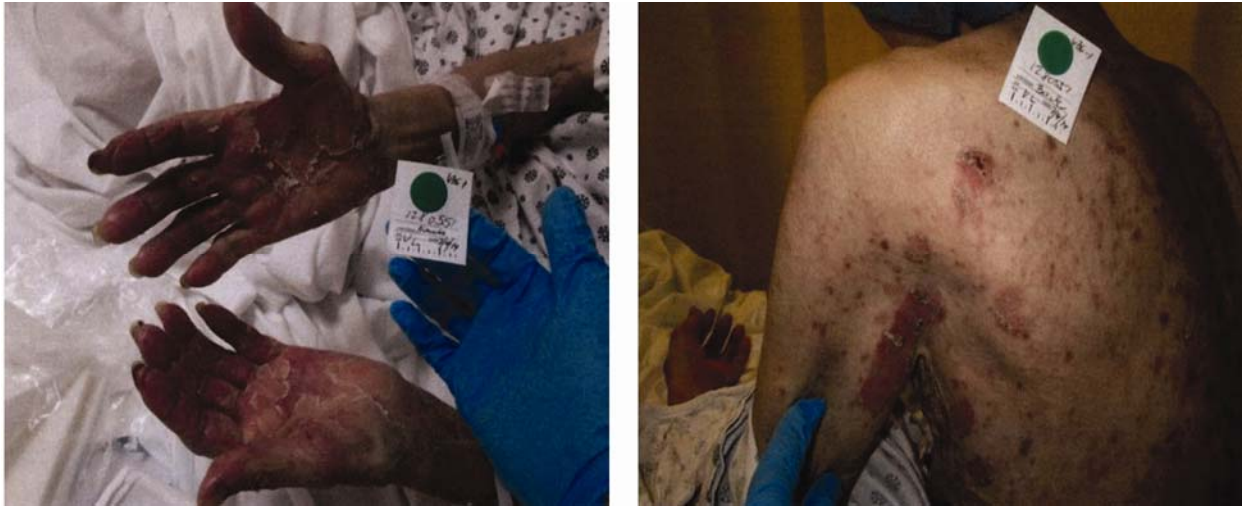
## 1 Introduction

Neoplasia-induced bullous diseases are described as a cell-mediated reaction against different epithelial antigens specifically Plakin proteins<sup>[1]</sup>. Failure to thrive, respiratory insufficiency among other complications can exacerbate the course of disease; however, no mortality was reported from increased emotional stress in affected patients<sup>[2, 3]</sup>. Takotsubo syndrome is a stress-induced cardiomyopathy, also prevalent in post-menopausal female even without coronary artery disease<sup>[4, 5]</sup>. Diagnosis of takotsubo cardiomyopathy usually relies on clinical history of a triggering stressor and classic echocardiogram findings in the absence of critical coronary arterial disease<sup>[5]</sup>. We present a case of paraneoplastic pemphigus that was complicated by takotsubo cardiomyopathy and expired during her hospital stay. In this case, we believe that the overwhelming disfigurement combined with lack of emotional support and/or psychotherapy led to development of fatal takotsubo cardiomyopathy.

## 2 Case presentation

This is a 71-year-old female patient of Korean-descent presented to the Emergency Department with painful mucocutaneous lesions mainly affecting oral mucosa and hands which have been worsening over a two-month period (see Figure 1). The patient reported poor oral intake and weight loss of fifteen pounds since the onset of symptoms. The patient had a

medical history significant for hepatitis B and asthma. Physical examination revealed yellow sticky discharge from the eyes, and genital labial ulceration. She was also found to have crusty eruption on lips and generalized vesicular eruptions on her hands, arms and back. Generalized lymphadenopathy was noted on exam as well. Laboratory workup showed white blood count (3.2 K/ $\mu$ l) with differential neutrophils (66.5%), lymphocytes (19.4%), eosinophils (4.6%) and monocytes (9.1%), hemoglobin (11.4 g/dl), potassium (3.3 mmol/L), and albumin (2.9 g/dl). Other work up including blood cultures, HIV and syphilis screening test were unremarkable. Contrast enhanced computed tomography scans of chest, abdomen and pelvis showed generalized lymphadenopathy mainly in the neck, intraperitoneal, and retroperitoneal regions.



**Figure 1.** Paraneoplastic pemphigus vulgaris presenting with mucocutaneous blisters and bullae in a B cell lymphoma patient

The patient was initially treated for presumed herpes simplex infection with intravenous acyclovir. Multiple punch biopsies of the skin confirmed intraepithelial blister formation associated with lichenoid/interface chronic inflammation in the dermis favoring erythema multiforme, drug eruption versus dermatopathic lymphadenitis. Herpes cultures from lip vesicles were negative and the patient did not show improvement on acyclovir. In view of spreading skin lesions and worsening of symptoms, she was then started on corticosteroids for bullous erythema multiforme versus paraneoplastic blistering eruption.

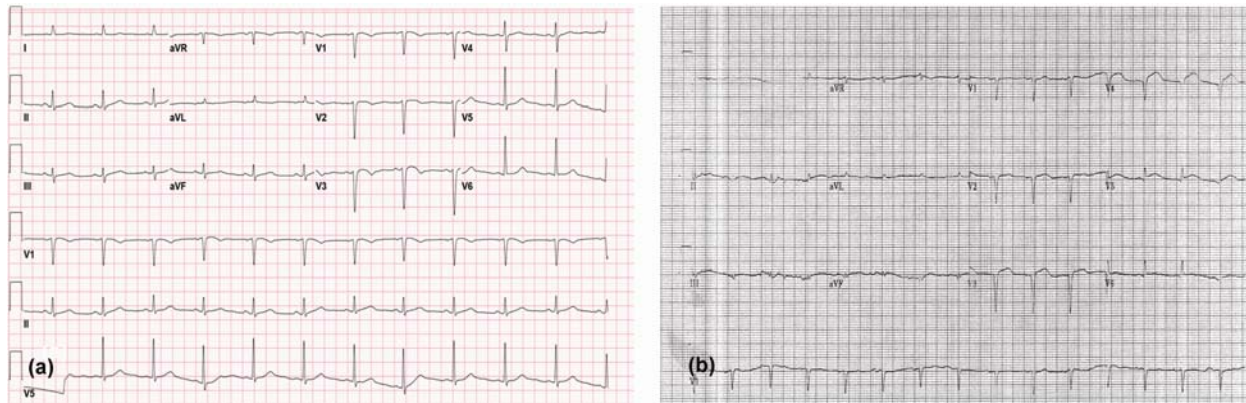
Core biopsies of cervical and axillary lymph nodes were inconclusive with no evidence of B-cell or T-cell lymphoproliferative disorder on flow cytometry studies. Further work up which included testing for human T-lymphotropic virus, polymerase chain reaction (PCR) testing of herpes simplex virus DNA subtypes in serum, autoimmune disorders, beta2 microglobulin test, HIV RNA testing and tuberculosis, were all negative.

A culture of bullae fluid revealed methicillin-sensitive staphylococcus aureus, with no acid fast bacilli or fungus growth noted. She was started on antibiotic therapy for infected bullous lesions. T-helper (CD4) count was found to be only 55; however CD4/CD8 ratio was preserved (0.42).

Fine needle aspiration of a retroperitoneal lymph node showed no lymphoid elements or malignant cells. However, retroperitoneal lymph node core biopsy revealed scattered B-cells and T-cells, but was negative for human herpes virus 8. Upon further testing, a left para-aortic lymph node core biopsy showed low grade B cell lymphoma suggesting marginal zone lymphoma and the patient was started on a course of Rituximab-Bendamustine. She showed improvement of skin and mucous lesions following chemotherapy, confirming the paraneoplastic origin of mucocutaneous lesions and discharge was planned.

The patient presented again to the Emergency Department one week after discharge with persistent complaints of painful ulceration of the mouth and skin, and the patient was re-hospitalized. Home medications included topical steroid cream

and lidocaine mouthwash that patient was using since her previous discharge. During the second day of her hospital stay, she complained of chest pain. The patient was found to have ST elevation on EKG leads V3-V5 (see Figure 2). Troponin T peaked to 0.162 ng/ml (normal range  $\leq 0.1$  mg/ml) while creatinine kinase remained normal. An echocardiogram showed severe systolic dysfunction with estimated ejection fraction of 20%-25%, hypokinesis of the inferior, anterior, septal, apical and mid-apical anterolateral wall compared to normal echocardiogram completed two months before. Catheter angiography was refused by the patient. Clinical presentation was attributed to takotsubo cardiomyopathy rather than acute coronary syndrome in view of typical echocardiogram findings and dissociation between severity of symptoms and EKG findings in comparison to the rise in cardiac enzymes. The patient expired during her stay in the Coronary Care Unit.



**Figure 2.** EKG showing new ST elevation in anterior and septal leads (b) compared to baseline EKG on patient's initial admission (a)

### 3 Discussion

Paraneoplastic pemphigus (PNP) is described in the literature as a cell-mediated reaction initiated against adhesive proteins leading to separation of skin layers, and is associated with different malignancies especially hematologic-related neoplasms such as Non-Hodgkin's lymphoma and chronic lymphocytic leukemia [1, 6]. Lesions almost always involve mucocutaneous regions such as the oral mucosa, nasopharynx, conjunctiva, and/or anogenital areas leading to many symptoms including pain and poor oral intake as the major debilitating symptoms [7]. Systemic effects of the disease are mainly mediated via antibody disposition in multiple organs especially causing restrictive bronchiolitis [2]. Mortality has been estimated to be two years with rates between 75%-90% caused mainly by sepsis and respiratory failure [3].

Takotsubo cardiomyopathy, known also as broken heart syndrome, is a stress-induced cardiomyopathy prevalent in post-menopausal women [4]. An influx of catecholamine enters the myocardium cells causing systolic dysfunction after experiencing intense psychological or physical stressors [5]. The event is characterized by transient systolic dysfunction of the apical and mid segments of the left ventricle on echocardiogram, findings that mimic myocardial infarction, but with the absence of obstructive coronary artery disease evidenced by coronary angiography [5, 8]. EKG changes typically include ST segment elevation, diffuse T-wave inversion, and abnormal QS wave alteration [9]. Diagnosis of stress cardiomyopathy should be suspected if symptoms and minor EKG changes are out of proportion to the degree of elevation of cardiac enzymes [9]. Coronary angiography may still show coronary atherosclerosis given the disease prevalence in the population at risk, which can be misleading in diagnosing this disease, especially in cases where transient occlusion is followed by subsequent spontaneous thrombus lysis [10, 11]. There's no reason to believe that an individual with established stable coronary artery disease would not also develop takotsubo cardiomyopathy. A previously published case series documented a 10% incidence of coronary artery disease in 97 Japanese patients diagnosed with takotsubo cardiomyopathy [12], while another study showed at least 50% stenosis of one epicardial coronary artery in seven patients that presented with takotsubo cardiomyopathy [13]. Although the Mayo Clinic has formulated a set of diagnostic criteria to recognize stress cardiomyopathy, the approach to patients present with ST elevation will remain the same [14].

The combination of bendamustine and rituximab was reported to cause a partially reversible cardiomyopathy in one case, however, takotsubo cardiomyopathy is not a documented side effect of the above mentioned chemotherapy regimen <sup>[15]</sup>. The possibility of chemotherapy triggering takotsubo cardiomyopathy cannot be entirely excluded though never reported before.

There is currently no literature of paraneoplastic pemphigus resulting in takotsubo cardiomyopathy. To our knowledge, this is the first case of its kind. We also find that it is worth studying the importance of psychotherapy and psychopharmacology in treating patients with significant medical comorbidities as part of their interdisciplinary plan of care.

Given high in-hospital mortality that can reach up to 8%, exploring treatment options such as psychopharmacology and psychotherapy can be used to decrease the occurrence of takotsubo cardiomyopathy related fatalities especially in prone populations with underlying overwhelming diseases <sup>[12]</sup>. In one study, preexisting depressive mood disorder was determined as an independent risk factor for 28-day mortality in medical ICU patients <sup>[16]</sup>. Either a diagnosis of major depressive disorder or a past history of depression independently predicted in-hospital mortality in medical inpatients <sup>[17]</sup>. Psychological intervention for patients with malignancies has been shown to have a great positive impact and improve patients' quality of life <sup>[18]</sup>. This case illustrates the psychosocial impact of serious skin diseases that can affect mortality even in view of a favorable prognostic malignancy.

## Acknowledgements

The authors wish to express their sincere gratitude to Fay Callejo, MPH and the research department in Coney Island Hospital for all the help and support.

## References

- [1] Oursler JR, Labib RS, Ariss-Abdo L, *et al.* Human autoantibodies against desmoplakins in paraneoplastic pemphigus. *J Clin Invest.* 1992; 89(6): 1775-1782. PMID:1601988 <http://dx.doi.org/10.1172/JCI115781>
- [2] Maldonado F, Pittelkow MR, Ryu JH. Constrictive bronchiolitis associated with paraneoplastic autoimmune multi-organ syndrome. *Respirology.* 2009; 14(1): 129-133. PMID:19144057 <http://dx.doi.org/10.1111/j.1440-1843.2008.01397.x>
- [3] Nousari HC, Deterding R, Wojtczak H, *et al.* The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med.* 1999; 340(8): 1406-1410. PMID:10228191 <http://dx.doi.org/10.1056/NEJM199905063401805>
- [4] Sharkey SW, Lesser JR, Zenovich AG, *et al.* Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation.* 2005; 111(4): 472-479. PMID:15687136 <http://dx.doi.org/10.1161/01.CIR.0000153801.51470.EB>
- [5] Wittstein IS, Thiemann DR, Lima JA, *et al.* Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med.* 2005; 352(6): 539-548. PMID:15703419 <http://dx.doi.org/10.1056/NEJMoa043046>
- [6] Kaplan I, Hodak E, Ackerman L, *et al.* Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. *Oral Oncol.* 2004; 40(6): 553-562. PMID:15063382 <http://dx.doi.org/10.1016/j.oraloncology.2003.09.020>
- [7] Wakahara M, Kiyohara T, Kumakiri M, *et al.* Paraneoplastic pemphigus with widespread mucosal involvement. *Acta Derm Venereol.* 2005; 85(6): 530-532. PMID:16396806
- [8] Volkhard K, Axel K, Katharina von H, *et al.* Apical and midventricular transient left ventricular dysfunction syndrome (takotsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest.* 2007; 132(3): 809-816. PMID:17573507 <http://dx.doi.org/10.1378/chest.07-0608>
- [9] Dec GW. Recognition of the apical ballooning syndrome in the United States. *Circulation.* 2005; 111: 388-390. PMID:15687123 <http://dx.doi.org/10.1161/01.CIR.0000155234.69439.E4>
- [10] Prasad A, Dangas G, Srinivasan M, *et al.* Incidence and angiographic characteristics of patients with apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: an analysis from a multicenter, international study of ST-elevation myocardial infarction. *Catheter Cardiovasc Interv.* 2014; 83: 343-348. PMID:22121008 <http://dx.doi.org/10.1002/ccd.23441>

- [11] Hoyt J, Lerman A, Lennon RJ, *et al.* Left anterior descending artery length and coronary atherosclerosis in apical ballooning syndrome (takotsubo/stress induced cardiomyopathy). *Int J Cardiol.* 2010; 145(1): 112-115. PMID:19573940  
<http://dx.doi.org/10.1016/j.ijcard.2009.06.018>
- [12] Todd Hurst R, Abhiram P, Wells Askew J, *et al.* Takotsubo Cardiomyopathy: A Unique Cardiomyopathy With Variable Ventricular Morphology. *J Am Coll Cardiol Img.* 2010; 3(6): 641-649 PMID:20541719  
<http://dx.doi.org/10.1016/j.jcmg.2010.01.009>
- [13] Gaibazzi N, Ugo F, Vignali L, *et al.* Tako-Tsubo cardiomyopathy with coronary artery stenosis: a case-series challenging the original definition. *Int J Cardiol.* 2009; 133(2): 205-212. PMID:18313156 <http://dx.doi.org/10.1016/j.ijcard.2007.12.037>
- [14] Bybee KA, Kara T, Prasad A, *et al.* Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern Med.* 2004; 141(11): 858-865. PMID:15583228  
<http://dx.doi.org/10.7326/0003-4819-141-11-200412070-00010>
- [15] Mulay S, Boruchov A. Recurrent and partially reversible cardiomyopathy occurring during treatment with bendamustine and rituximab. *Leuk Lymphoma.* 2015; 56(3): 805-807. PMID:24913498 <http://dx.doi.org/10.3109/10428194.2014.931954>
- [16] Wewalka M, Warszawska J, Strunz V, *et al.* Depression as an independent risk factor for mortality in critically ill patients. *Psychosom Med.* 2015; 77(2): 106-113. PMID:25626990 <http://dx.doi.org/10.1097/PSY.0000000000000137>
- [17] von Ammon Cavanaugh S, Furlanetto LM, Creech SD, *et al.* Medical illness, past depression, and present depression: a predictive triad for in-hospital mortality. *Am J Psychiatry.* 2001; 158(1): 43-48. <http://dx.doi.org/10.1176/appi.ajp.158.1.43>
- [18] Rovner BW, German PS, Brant LJ, *et al.* Depression and mortality in nursing homes. *JAMA.* 1991; 265(8): 993-996. PMID:1992213 <http://dx.doi.org/10.1001/jama.1991.03460080063033>