Invited Editorial

Bronchopleural fistula treatment: From the archetype of surgery to the future of stem cell therapy

Bronchopleural fistula (BPF) is a pathological connection between the airway and the pleural space that may develop after lung resection[1] or following thoracic traumas, complications of infective pleuropulmonary diseases or on account of the rupture of emphysematous bullae, as reported by Goyal and collegues in the present number of Lung India.[2]

The incidence of BPF in thoracic surgery ranges from 1 to 4%, but its mortality rate ranges from 12.5 to 71.2%. It may be caused by incomplete bronchial closure, impediment of bronchial stump wound healing or stump destruction by residual neoplastic tissue.[1]

The clinical effect of impaired bronchial stump healing after anatomic lung resection may culminate in a life-threatening septic and ventilatory catastrophe.[3] For many patients with empyema, the presence or absence of a fistula makes the difference between recovery, chronicity or death.[4]

For all these reasons, bronchial stump dehiscence is still the most feared complication following curative lung resection,[5] and although many technical precautions are taken by thoracic surgeons while performing major pulmonary resection,[6] bronchopleural fistula remains a hard challenge to face.

Every skilled and honest thoracic surgeon has his personal series of post-resectional bronchopleural fistulas, mainly dependent on the volume of extended resections performed (completion pneumonectomy, post chemoradiotherapy pulmonary resection, extended resection) rather than on the personal skill or suture technique. In fact — as any thoracic surgeon knows — the most precise stitch or the most careful lymph node dissection is often not enough to prevent such a serious complication in many scenarios.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/0970-2113.152613

From the beginning of modern thoracic surgery, many complex procedures have been advocated as salvage therapy for bronchopleural fistula, as reported by Goyal and collegues: Muscle flap closure, completion lobectomy or pneumonectomy, and thoracoplasty are only some examples of the surgical options; open window thoracostomy — consisting of rib resection and daily medications by gauzes — is one of the most effective rescue treatments, but on the other hand, it is one of the most aggressive and psycologically disabling operations a patient can undergo [Figure 1a and b].

With the advent of flexible bronchoscopy, a plethora of endoscopic treatments have been proposed for bronchopleural fistula closure, fibrin glue local injection and stenting being the most reported;[7,8] however, only small caliber fistula can be managed by a pure bronchoscopic approach, the failure percentage being not negligible.

Development of cell therapies and bioengineering approaches for lung diseases has rapidly progressed over the past decade.[9] A number of early reports initially suggested that bone marrow-derived cells [Figure 2], including mesenchymal stem cells (MSCs) and other populations, could structurally engraft as mature differentiated airway and alveolar epithelial cells or as pulmonary vascular or interstitial cells.[10] Some recent reports continue to suggest that engraftment of the donor-derived airway can occur with several different types of bone marrow–derived cells.[11]

Mesenchymal stem cells from the bone marrow, adipose and placental tissues, and other origins have been widely

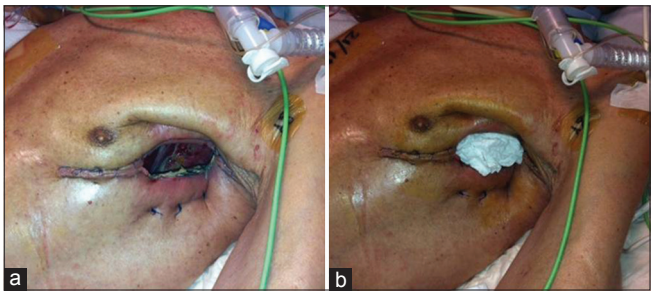

Figure 1: Open-window thoracostomy in an Intensive Care Unit (ICU) patient suffering from post-resectional bronchopleural fistula following left pneumonectomy before (a) and after (b) chest cavity filling by using gauzes

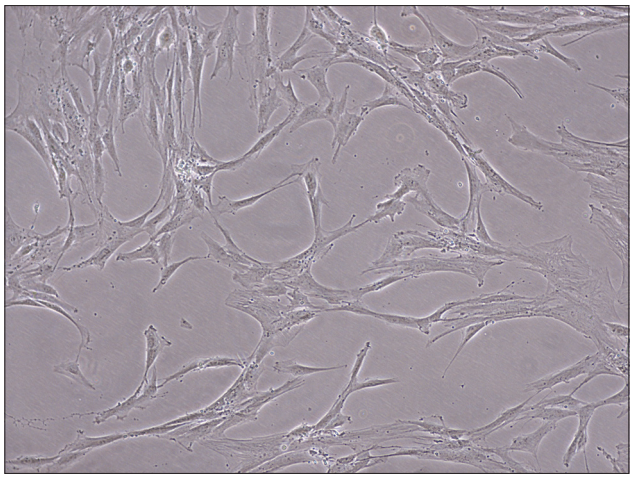

Figure 2: Morphology of the bone marrow mesenchymal stem cells at passage 1

investigated for their immunomodulatory effects in a broad range of inflammatory and immune diseases.[12] However, the mechanisms of MSC actions are only partially understood. In addition to the paracrine actions of soluble peptides and other mediators, a growing body of data suggests that release of episomal or microsomal particles by MSC can influence the behavior of both surrounding structural and inflammatory cells.[9] A recent report suggests that MSC may also promote repair by activation of endogenous distal lung airway progenitor cell populations in mouse models.[13]

Mesenchymal stem cells can also exert an effect on lung inflammation and injury through primary interactions with the immune system rather than through direct actions in the lung in particular, when the cells are systemically delivered.[9]

Our previous preclinical airway experiments on goats demonstrated that bronchoscopic transplantation of bone marrow–derived mesenchymal stem cells (BMMSC) effectively closed the BPF by extraluminal fibroblast proliferation and collagenous matrix development.[14] Encouraged by experimental bronchial wall restoration in large animals, and by functional human organ replacement elsewhere,[15] we recently undertook autologous BMMSC bronchoscopic transplantation to treat a patient, who developed BPF after right extrapleural pneumonectomy for malignant mesothelioma.[16]

Although the bronchoscopic view clearly showed an endoluminal complete bronchial restoration, we could not exclude the idea that an external healing process may have significantly contributed to the BPF closure. Hence, the clinical resolution of symptoms may be due in part to a physiological healing process rather than a healing induced by bronchoscopic MSC transplantation. Moreover, the caliber of the BPF in our case accounted for about 30% of the stump length. It could be argued that a larger caliber fistula may not have benefited from BMMSC transplantation because of the lack of a healthy bronchial scaffold in which the cells could be injected.[16]

In conclusion, although cellular therapies may represent a new interesting therapeutic option for airway fistula closure, before they can be routinely used as a treatment, more basic research is needed and standard surgical and conservative approaches still remain the first theraputic options.

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How to cite this article: Petrella F, Spaggiari L. Bronchopleural fistula treatment: From the archetype of surgery to the future of stem cell therapy. Lung India 2015;32:100-1.