Original Article

Experience with Treatment of Pulmonary Alveolar Proteinosis from a Tertiary Care Centre in North India

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ABSTRACT

Background. Pulmonary alveolar proteinosis (PAP) is a disorder characterised by accumulation of lipids and proteins in the alveoli, with the resultant symptoms ranging from indolent subclinical disease to progressive respiratory failure.

Methods. We retrospectively studied five patients with PAP managed at our center between January 2007 and April 2010, with whole lung lavage (WLL) and/or subcutaneous granulocyte macrophage-colony stimulating factor (GM-CSF) therapy. Patients undergoing WLL under general anaesthesia were supplemented with three months of GM-CSF therapy. Pre- and post-lavage symptom assessment was performed with a 10-point, symptom-based visual analogue scale.

Results. Their mean age was 37.6±7.0 years; there were four males. Diagnosis of PAP [idiopathic (n=3); secondary to *Nocardia* (n=1)] was established by surgical lung biopsy in four patients who presented with respiratory failure. Three patients with idiopathic PAP (n=3) were treated with a combination of GM-CSF and WLL; one patient with secondary PAP was treated with antibiotics alone. In another patient transbronchial lung biopsy was used to diagnose PAP and GM-CSF alone was administered. All patients were followed up for a median period of two years (range 0.5-3 years). Significant improvement was achieved in all the patients with therapeutic WLL and/or GM-CSF.

Conclusions. Whole lung lavage appeared to be an effective and safe therapy in patients with PAP. Efficacy of simultaneous administration of GM-CSF and WLL in the treatment of PAP merits further study.

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Key words: Pulmonary alveolar proteinosis, Whole lung lavage, Granulocyte macrophage-colony stimulating factor.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterised by progressive accumulation of periodic acid Schiff (PAS) positive lipoproteinaceous material, that is chemically and ultrastructurally similar to normal surfactant, in the alveoli. The clinical presentation of PAP ranges from incidental diagnosis in an asymptomatic patient to severe disease presenting with respiratory failure. The natural course of the disease is variable but the prognosis is generally favourable; frequently with spontaneous resolution.[1,2] Idiopathic or autoimmune PAP constitutes more than 90% of all reported cases of acquired PAP.[3] Less commonly PAP may also occur in patients with underlying infections or malignancy.[4] Physiologically, the alveolar surfactants are tightly regulated by the balanced production and catabolism by alveolar epithelial cells and macrophages, augmented by action of granulocyte-macrophage-colony stimulating factor (GM-CSF) on its terminal differentiation.[5] Demonstration of GM-CSF autoantibodies in plasma and alveolar fluid of patients with idiopathic PAP suggest their primary role in pathogenesis.[6] Lung lesions are characteristically distributed in a geographical pattern involving the whole lung. The classical appearance of PAP on high resolution computerised tomography (HRCT) of the chest includes interlobular septal thickening superimposed on patchy ground glass opacities giving a "crazy-paving" pattern.[7] The chest radiograph correlates well with the restrictive ventilatory defect and reduced diffusing capacity seen in PAP.[8] Well preserved alveoli filled with proteinaceous material are typically seen on histopathology.[9]

Whole lung lavage (WLL) has remained the standard of care for patients with PAP, in the absence of any proven effective pharmacotherapy.[10] Whole lung lavage not only physically removes extra-

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proteinaceous material from alveoli, but also restores migration and phagocytic functions of alveolar macrophages secondary to the bulk removal of local anti-GM-CSF antibody.[11,12] Pharmacotherapy with exogenous systemic GM-CSF is a promising new approach in the treatment of adult patients with PAP.[13,14] *To the best of our knowledge, the use of GM-CSF alone or in combination with WLL in the Indian population has not been previously reported*. Herein, we report our experience with WLL and GM-CSF in patients with PAP.

MATERIAL AND METHODS

We reviewed the case records of patients undergoing treatment for PAP at our centre over a four-year period (January 2007 to December 2010). Patients suspected to have PAP were extensively evaluated for any underlying secondary cause. Once these were excluded, diagnosis was confirmed through lung biopsy (either surgical or bronchoscopic). Patients were prepared for WLL if they had persistent or progressive respiratory failure or demonstrated exercise desaturation. Subcutaneous GM-CSF was used as adjunct in patients planned for WLL, and as the sole therapy in patients without indication for WLL. Pre- and post-treatment symptoms were assessed on a visual analogue scale from 0-100 mm (0=no symptom; 100=severe symptoms).

We also systematically reviewed reported cases of PAP from India by searching the PubMed and IndMed databases. The patients included in this systematic article had typical clinical and radiological findings of PAP and the diagnosis was confirmed histologically.

Briefly, WLL was performed under general anaesthesia as per standard guidelines, with continuous physiological monitoring. Inhalational anaesthetic agents were avoided to prevent the inhibition of hypoxic pulmonary vasoconstriction. Swan-Ganz catheters were used to monitor pulmonary artery capillary wedge pressure and cardiac output. Femoral arteriovenous access was secured and an extra-corporeal membrane oxygenator was kept stand-by. Patients were intubated with left sided 35 F double lumen endotracheal tube (DLT, BronchoCath®, Mallinckrodt Medical, Inc., Livermore, CA) to achieve lung isolation during lavage. Subsequently, the lung to be lavaged was made non-dependent by giving 15° to 30° tilt to the table, and the corresponding endotracheal tube lumen clamped to effect lung collapse. The side of the double lumen endotracheal tube to the non-dependent lung planned for lavage was clamped to allow the rapid absorption of the oxygen causing collapse of this lung. This lung was then gravity filled to total lung capacity with 750-1000 mL aliquots of saline solution warmed to body temperature. Subsequently, the draining limb of Y-connector was opened and fluid was allowed to drain with gravity, supplemented by manual percussion of the chest to maximise fluid return. The procedure was repeated until the effluent turned clear from the initial turbid appearance. During this period, the non-lavaged lung was independently ventilated using 100% oxygen. Upon completion of the procedure, the tracheobronchial tree on the lavaged side was thoroughly suctioned to clear the airways of excess residual saline using fiberoptic bronchoscopy. Once the adequate gas exchange capabilities were established on the lavaged side, patient was turned to the opposite side and the other lung was lavaged using the same procedure.

RESULTS

Five patients underwent treatment for PAP (Table 1). All patients presented with dyspnoea and cough. One of them had PAP secondary to *Nocardia*. Hypoxaemic respiratory failure was present in four patients necessitating ventilatory support.

Table 1. Baseline characteristics and ultimate management of the patients with PAP

No.	Age (in years)/ Gender	Clinical Features	Duration of Symptoms	Diagnosis	Aetiology	Treatment	Follow-up (in years)
1	46/F	Dyspnoea, cough, respiratory failure	4 months	OLB	Idiopathic	B/L simultaneous WLL with ECMO + GM-CSF	3
2	42/M	Dyspnoea, cough, respiratory failure	7 months	OLB	Idiopathic	B/L sequential WLL + GM-CSF	2
3	38/M	Dyspnoea, cyanosis, respiratory failure	2 months	OLB	Idiopathic	B/L sequential WLL + GM-CSF	2
4	28/M	Dyspnoea, fever, loss of appetite, respiratory failure	10 months	OLB	Secondary	Trimethoprim-sulfamethoxazole	2.5
5	34/M	Dyspnoea, cough	4 years	BLB	Idiopathic	Subcutaneous GM-CSF	0.5

F=Female; M=Male; OLB=Open lung biopsy; BLB=Bronchoscopic lung biopsy; B/L=Bilateral; WLL=Whole lung lavage; ECMO=Extra-corporeal membrane oxygenation; GM-CSF=Granulocyte monocyte-colony stimulating factor.

Three patients presenting with respiratory failure underwent WLL (Table 2). Sequential bilateral WLL was performed in a single setting in two patients while simultaneous bilateral WLL under total cardio-pulmonary bypass was undertaken in one patient due to worsening unresponsive hypotension and hypoxaemia. These patients were started on subcutaneous GM-CSF (5µg/kg body weight) preoperatively and continued for three months after the procedure. Technically successful WLL was performed in all the patients, with rapid improvement in the symptoms immediately after the procedure. All patients required mechanical ventilation for at least 24 to 72 hours. One patient developed spontaneous tension pneumothorax on the first day following WLL, and was managed with tube thoracostomy. One patient who presented with respiratory failure was diagnosed to have secondary PAP due to *Nocardia* on surgical lung biopsy and was managed with oral trimethoprim-sulfamethoxazole combination therapy alone without WLL or GM-CSF. One mildly symptomatic patient diagnosed with bronchoscopic biopsy was managed with subcutaneous GM-CSF alone. All the patients were followed up for a median duration of two years (range 0.5-3 years) and are asymptomatic with improvement both clinically and radiologically.

Table 2. Whole lung lavage characteristics of three patients

No.	WLL (Liters)		Exchanges	Duration (in minutes)	Haemoglobin (gm/dL)		Haematocrit (%)		PaO_2 (mmHg) on Room Air		VAS		Complications
	Right Lung	Left Lung			Pre-lavage	Post-lavage	Pre-lavage	Post-lavage	Pre-lavage	Post-lavage	Pre-lavage	Post-lavage	
1	26.8*		22	260	17.6	13.8	49.2	42.4	42.6	89.4	10	80	None
2	14	12	25	190	16.0	15.2	47.4	47.0	58.6	90.8	25	88	Tension pneumothorax
3	13	12	23	210	21.0	128	52.2	44.0	56.8	92.7	22	74	None

WLL=Whole lung lavage; PaO_2=Arterial oxygen tension; VAS=Visual analogue scale score.
* Simaltaneous bilateral lung lavage was performed; volumes for the right and left lung were not calculated separately.

Patient 1. A 46-year-old previously healthy female was admitted with complaints of worsening dyspnoea and cough of four months. HRCT of the chest revealed geographical areas of interlobular septal thickening superimposed on a background of ground-glass opacities involving the entire lung (Figure 1). Arterial blood gas (ABG) analysis showed hypoxaemic respiratory failure. She was mechanically ventilated with positive end-expiratory pressure (PEEP) of 20cm H_2O and fraction of inspired oxygen (FIO_2) of 1.0 following initial failure of non-invasive ventilation (NIV). An open lung biopsy confirmed the diagnosis of PAP (Figure 2). She was taken up for WLL but immediately after the start of first aliquots of saline infusion she developed hypotension, arterial desaturation and rapidly worsening hypercapnia that remained unresponsive to routine measures. As a rescue measure patient was initiated on total cardio-pulmonary bypass. Once the patient was haemodynamically stable, bilateral simultaneous WLL was performed keeping the saturation close to 88% throughout the procedure. Post-procedure recovery was rapid and the patient was extubated on the third day. During the subsequent three years she remained asymptomatic with marked radiological and functional improvement (Figure 3).

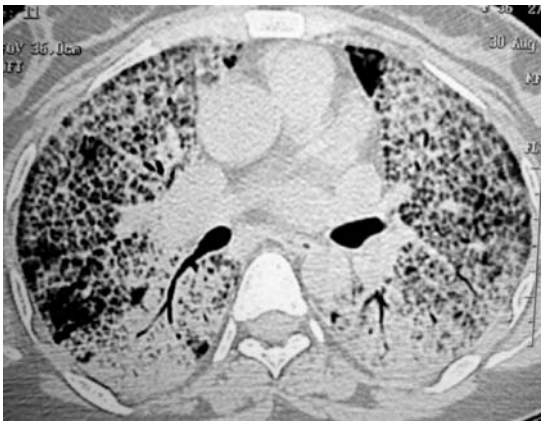

Figure 1. HRCT of chest of a patient with pulmonary alveolar proteinosis demonstrating characteristic crazy-paving appearance.

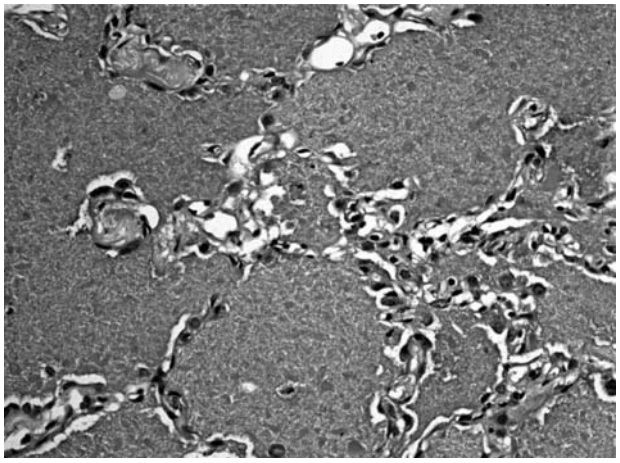

Figure 2. Photomicrograph showing eosinophilic granular material filling alveolar spaces with intact alveolar septum and little reaction in alveolar walls (Haematoxylin and eosin×100).

Patient 2. A 42-year-old male presented to the emergency department with progressive respiratory discomfort and cough of seven months duration.

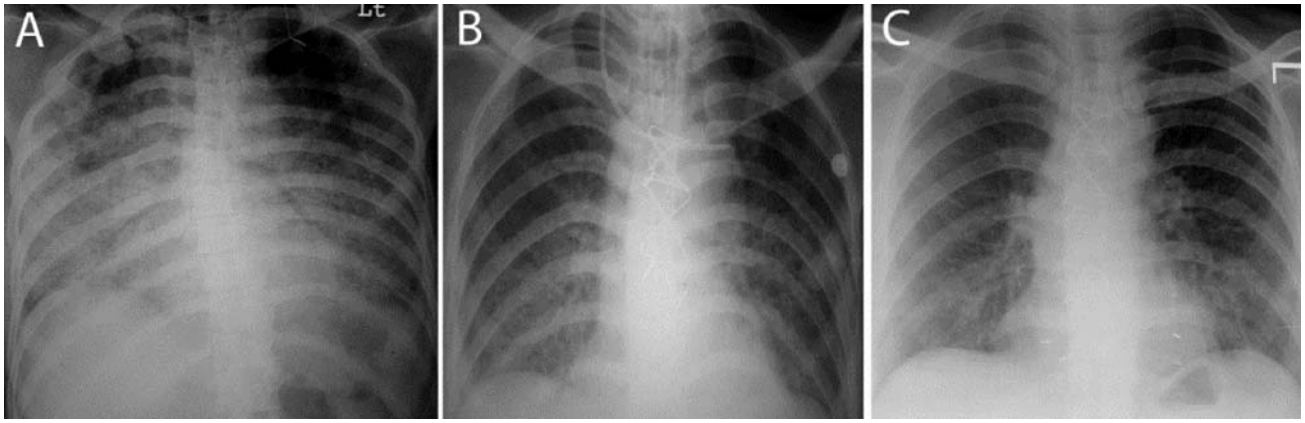

Figure 3. Serial chest radiographs of a patient with pulmonary alveolar proteinosis: at initial presentation (A); immediately after whole lung lavage (B); and at follow-up after two years (C).

He had severe hypoxaemia, which could not be optimally corrected despite mechanical ventilation using 100% oxygen and PEEP of 15. HRCT of the chest showed a crazy paving appearance, and diagnosis of PAP was confirmed on surgical lung biopsy. Bilateral sequential WLL in a single session was performed. Rapid improvement in ventilatory parameters and a decrease in the ventilatory requirement was observed. However, on the second day, patient developed spontaneous tension pneumothorax that was managed with tube thoracostomy under water-seal. The patient was extubated the next day. At the time of last follow-up at two years, he continued to remain asymptomatic.

Patient 3. A 38-year-old male, farmer presented with two months history of cyanosis and breathlessness. ABG analysis revealed severe hypoxaemia [arterial oxygen tension (PaO_2) 44 mmHg on room air]. HRCT chest showed "crazy paving" pattern. Laboratory investigations revealed haemoglobin 21g/dL and marked thrombocytosis. Detailed haematological work-up including bone marrow biopsy was done to rule out a myeloproliferative disorder. He was initially managed with NIV. However, his respiratory status deteriorated over a week and he required mechanical ventilatory support. Open lung biopsy was done 15 days after hospitalisation and diagnosis of PAP was confirmed. Patient was put on GM-CSF therapy and bilateral sequential WLL was performed. Subsequent recovery was fast and his haemoglobin levels came down to 12g/dL. Patient was extubated on the seventh day. On follow-up after two years, patient is asymptomatic and is maintaining adequate oxygenation on room air.

Patient 4. A 28-year-old male presented with progressive dyspnoea and intermittent fever for 10 months. His oxygen saturation on room air was 74%, which fell to 66% during physical examination. Typical patchy crazy paving pattern, more so in the left lung, was evident on HRCT of the chest. He improved with NIV support but failed in weaning attempts. Initial work-up for the secondary PAP was inconclusive, and thus, he was subjected to open lung biopsy. Histopathology revelaed PAS-positive alveolar filling with intact septa, and typical crooked, branching, beaded, gram-positive organisms consistent with *Nocardia*. He was started on oral trimethoprim-sulfamethoxazole, and responded in five days with a decrease in the ventilatory requirement. He was extubated on day seven and discharged after one week. Oral therapy was stopped at six months. He remains asymptomatic after more than two years of follow-up.

Patient 5. A 34-year-old male presented with dyspnoea on exertion for four years, with symptomatic worsening over the past four months. He was a life time non-smoker, and had no environmental exposure to dust. HRCT of the chest done four years back showed interlobular septal thickening with patchy ground glassing in the perihilar regions that progressed and involved the entire lung in the fresh HRCT. Oxygen saturation while breathing room air was 93% with maximum fall of 4% on exercise. Bronchoscopic lung biopsy showed typical picture of PAP. Because of the slowly progressive disease and only mild symptoms, he was started on subcutaneous GM-CSF 5µg/kg body weight. At six months follow-up, his symptoms has improved but radiological improvement was not evident.

A systematic search of the Indian literature yielded five reports of PAP (Table 3).[15-19] Dyspnoea and cough were the most common presenting features in these patients. Except for the one patient who received WLL in two sessions, all received bilateral simultaneous WLL in a single setting. No procedure related complication has been reported. One publication[20] documented secondary PAP, the

Table 3. Patient's characteristics and response to treatment in cases with PAP reported from India

Reference	Age (in years/ Gender	Symptoms	Smoking	Diagnosis	Aetiology	Treatment	Baseline PaO_2	Post WLL PaO_2	Response
Dixit *et al*[15]	14/M	Dyspnoea, cough, fever	No	Bronchoscopic aspiration lavage	NA	B/L sequential WLL	60.0	NA	Clinical response
Indira *et al*[16]	53/M	Dyspnoea, cough	No	OLB	Idiopathic	B/L sequential WLL	63.2	74.7	Clinico-radiological response
Kumar *et al*[17]	45/F		NA	OLB	NA	B/L sequential WLL	56.0	77.0	Clinico-radiological response
Nandkumar *et al*[18]	43/M	Dyspnoea	NA	NA	NA	Single lung lavage in two settings	52.1	62.0	Clinical response
Jayaraman *et al*[19]	26/M	Dyspnoea, cough	NA	OLB	Idiopathic	B/L sequential WLL	NA	NA	Clinico-radiological response

PAP=Pulmonary alveolar proteinosis; PaO_2=Arterial oxygen tension; WLL=Whole lung lavage; M=Male; F=Female NA=Not available; OLB=Open lung biopsy; B/L=Bilateral.

diagnosis of which was made on post-mortem lung biopsy and no treatment was given for PAP.

DISCUSSION

Our experience suggests that WLL is an effective method of relieving respiratory insufficiency in patients with PAP presenting with hypoxaemic respiratory failure. Combining exogenous therapy with GM-CSF as an adjunct to WLL may prevent long-term disease recurrence. However, more data is required before this approach can be generalised.

WLL has remained an established and effective method in the treatment of PAP, since an initial description by Ramirez nearly five decades ago.[21] Over the years, this crude method has been refined and modified in different centers to produce a better outcome with minimal procedural difficulty. Successful completion of sequential bilateral WLL in the same session is the current standard of WLL due to its safety, reduced length of hospital stay and less operative morbidity common with multiple sessions of WLL. Application of physical therapies in the form of manual percussion, vibration, and compression of the chest to mobilise secretions from peripheral airways to the central airway during the gravity drainage of the lavage was utilised in all of our patients to prevent hypoxaemia during this phase of WLL.[22-24] Partial and total cardiopulmonary bypass with extra-corporeal membrane oxygenation (ECMO) is frequently used in paediatric population during the WLL; however, its use in adult patients is limited.[25] Nevertheless, the use of ECMO during WLL facilitates adequate gas exchange in the setting of severe respiratory failure when lung lavage cannot be otherwise safely accomplished, as seen in one of our patient. Total cardiopulmonary bypass was utilised in one of our patient as a rescue measure when all other methods failed; however, it allowed us to perform lavage of both the lungs in the same setting.

The outcome of WLL depends on the timing and indication of the lavage, which is typically performed in a symptomatic patient with dyspnoea limiting daily activity and progressive deterioration of arterial oxygenation. Hence, PaO_2 less than 65 mmHg, alveolar arterial oxygen gradient [$P(A–a)O_2$] more than 40 mmHg or a shunt fraction greater than 10%-12% are used as a threshold for therapeutic lavage in many centres.[2,26] The occurrence of respiratory failure in all of our patients at presentation necessitated WLL as the only treatment option to rapidly correct the underlying pathophysiological abnormalities. Because of lack of established response criteria for therapeutic lavage, clinical, functional and radiological improvement were used as indicators of response following WLL in all of our patients.[1,2,26,27] Although median duration of clinical benefit from lavage is around 15 months with majority requiring repeat lavage at some point of their natural course of the disease, none of our patient had recurrence of symptoms on last follow up.[3] Rapid clinical improvement in all the patients in this series confirms that despite the complex procedure requiring prolonged general anaesthesia, WLL remains the gold standard in the treatment of PAP with better outcome and survival compared to those without WLL.[3]

One of our patients had secondary PAP related to *Nocardia* infection, and was managed only with antimicrobial therapy. It is well known that infections such as nocardiosis or tuberculosis can result in secondary PAP, and respond excellently to specific antimicrobial treatment. The problems in

idiopathic PAP are more complex and less well understood. The recent recognition of functional GM-CSF deficiency in the pathogenesis of autoimmune PAP led to the initial therapeutic trial of GM-CSF in a patient failing to achieve remission with repeated lavage.[28] Subsequent usage of subcutaneous or inhaled GM-CSF in increasing number of patients reaffirmed its effectiveness in autoimmune PAP. However, only half of the treated patients actually benefited from GM-CSF therapy in the reported series and many of them either required repeated GM-CSF or dose escalation to achieve a response.[28,29] The reasons for such a differential response of GM-CSF may be related to therapeutic response that requires delivery of adequate amounts of GM-CSF to overcome the neutralising capacity of endogenously produced anti-GM-CSF antibodies as well as the compartmentalisation phenomenon preventing access of GM-CSF to the alveolar spaces due to densely accumulated surfactant. Moreover, in all these studies, GM-CSF has been used either as a sole therapy or a rescue therapy in patients with failing WLL. In our study, we combined GM-CSF in all the patients undergoing WLL whereas it was the sole therapy in one mildly symptomatic patient. The encouraging outcome on long term follow-up with clinico-physiological improvement without recurrence could also suggest a benefit of combination therapy. By removing bulk of anti-GM-CSF antibodies in lavage fluid, WLL probably augments the action of GM-CSF therapy in restoring normal alveolar clearance mechanism by inducing terminal differentiation of alveolar macrophages. However, in our series, as the benefit lasted for several years despite the fact that GM-CSF therapy was used only for three months, the possibility of spontaneous resolution of the disease cannot be ruled out. Thus, this novel approach requires further studies to confirm its benefit including use of control group. This combination therapy is especially useful in resource limited countries where the therapy of PAP is limited by the lack of centres performing WLL. Reduction in the requirement for repeated WLL by combination approach is a promising option in the treatment of PAP. The major limitation of this study apart from the small size is the lack of demonstration of anti-GM-CSF antibodies. However, due to lack of availability of such an assay, we were unable to perform this test.

CONCLUSIONS

Whole lung lavage is an effective therapy in the management of PAP. Patients need confirmation of the diagnosis by tissue biopsy, followed by clinico-physiological assessment to define the severity of the disease, before they are subjected to this procedure. Asymptomatic patients can be observed with periodic physiological assessment for deterioration. In milder disease a therapeutic trial of GM-CSF alone to induce the remission and vigilant observation may obviate the need for WLL. WLL supplemented with GM-CSF therapy is a potentially promising option in patients with severe autoimmune PAP.

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