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Brief Report

The bronchial cast syndrome after the Fontan procedure: further evidence of its etiology

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Abstract We describe a three-year-old boy who presented with recurrent expectoration of bronchial casts six months following creation of a fenestrated lateral tunnel Fontan circulation for pulmonary atresia with intact ventricular septum. Cardiac catheterization demonstrated elevated central venous pressure with two areas of stenosis within the Fontan circuit, specifically at the junction of the right superior caval vein and the right pulmonary artery, and between the atrial baffle and the right superior caval vein. Insertion of Palmaz stents in these areas resulted in a reduction in central venous pressure, and a transient reduction in production of casts. Eight weeks after catheterization, however, he produced further casts, which resulted in hypoxia, respiratory arrest and death. We reviewed the autopsied specimens obtained from patients with the Fontan circulation over an eleven-year period at our institution in order to ascertain the prevalence of subclinical production of bronchial casts. We found no casts in the thirteen patients examined. Hemodynamic assessment is vital in all patients who develop this syndrome, and should be the primary focus of investigation, rather than solely directing efforts at lysis of casts.

Keywords: Functionally univentricular circulation; hemodynamics; plastic bronchitis.

So-called plastic bronchitis is a rare condition consisting of recurrent expectoration of bronchial casts.[1] The first clinical description of this phenomenon in association with congenital cardiac disease was by given by Bettmann in 1902.[2] It has been described most commonly in association with the Fontan procedure.[3–5] Seear classified bronchial casts into "inflammatory" and "acellular" types, which are typically associated with cyanotic congenital heart disease in cases with severe cardiac decompensation.[1] The etiology remains unknown, although elevation of central venous pressure has been implicated. We report a patient with Fontan circulation who developed recurrent bronchial casts in association with elevated central venous pressure. The problem transiently improved following reduction of central venous pressure. We also reviewed post-mortem specimens from all patients with a Fontan circulation at our institution who died over an 11-year period to assess whether there was subclinical generation of bronchial casts.

Case report

A boy was diagnosed with pulmonary atresia with intact ventricular septum on the first day of life. He underwent placement of a right modified Blalock-Taussig shunt on the fourth day of life. At 7 months of age, he underwent creation of a bidirectional Glenn shunt, and subsequently creation of a fenestrated lateral tunnel Fontan circulation at two years of age. Cardiac catheterization prior to the Fontan operation showed the mean pulmonary arterial pressure was 15mmHg, and pulmonary arteriolar resistance was 2.0 Wood units. The Fontan procedure was complicated by persistent pleural effusions, which required continued drainage via

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chest tubes for four weeks. The pleural fluid was transudate in nature, with no evidence of lymph. He had no previous history of reactive airway or suppurative lung disease, although he did have a history of recurrent otitis media. There was no clinical evidence of allergic bronchopulmonary aspergillosis. His medications included lasix, digoxin and captopril.

On examination at 2–1/2 years of age, his oxygen saturation was 75% when breathing room air. His heart rate was 90 beats per minute with normal sinus rhythm, the respiratory rate was 20 breaths per minute, and the blood pressure measured 110/65mmHg in his right arm. The jugular venous pulse was elevated 2cm above the clavicle. There were midline sternotomy and right thoracotomy scars. The precordium was quiet. The apex beat was palpable in the left fifth intercostal space in the midclavicular line. On auscultation, there was a single first and second heart sound, with no additional heart sounds or murmurs. There was good air-entry bilaterally, but on auscultation there was a distinctive flapping sound similar to that of a "sail in the wind". There was a 3cm liver palpable below the right costal margin. Chest radiography demonstrated a normal cardiothoracic ratio with non-specific diffuse infiltrates in the right upper lobe. The electrocardiogram demonstrated left atrial rhythm and right ventricular hypertrophy with strain. Six months after the Fontan operation, he began to expectorate bronchial mucinous casts, often presenting them to this mother for inspection. He continued to expectorate a bronchial cast approximately every 2 weeks. Six months after developing such plastic bronchitis, he was admitted with a respiratory arrest. He required emergent bronchoscopy and broncho-alveolar lavage. A cast was found in the proximal trachea, which was occluding both the left and right main bronchuses and extended through 6 bronchial generations (Fig. 1). Light microscopic examination of the cast material (Fig. 2a-c) showed a paucicellular fibrin and mucin cast containing very small numbers of macrophages, eosinophils, neutrophils, erythrocytes, and squames, as well as unidentifiable mononuclear cells. Small numbers of lipid droplets were also identified in the material. He underwent surveillance bronchoscopy, which demonstrated no further casts or inflammatory changes. Despite this, he continued to produce casts approximately every 2 weeks. He was commenced on albuterol nebulizers and low dose oral clarithromycin with little clinical response. Immunoglobulins were normal and a sweat test was negative. The T-cell percentage count was low, and natural killer cells were elevated, although the absolute number of lymphocytes was normal for host defense. His T-cell mitogen stimulation was also low. Given these minor abnormalities in T-cells, flourescent-in-situ hybridization was performed for 22q11 deletion, which was negative. There was no evidence of α-1 antitrypsin in the stools. Holter examination revealed normal sinus rhythm with occasional sinus bradycardia and junctional escape.

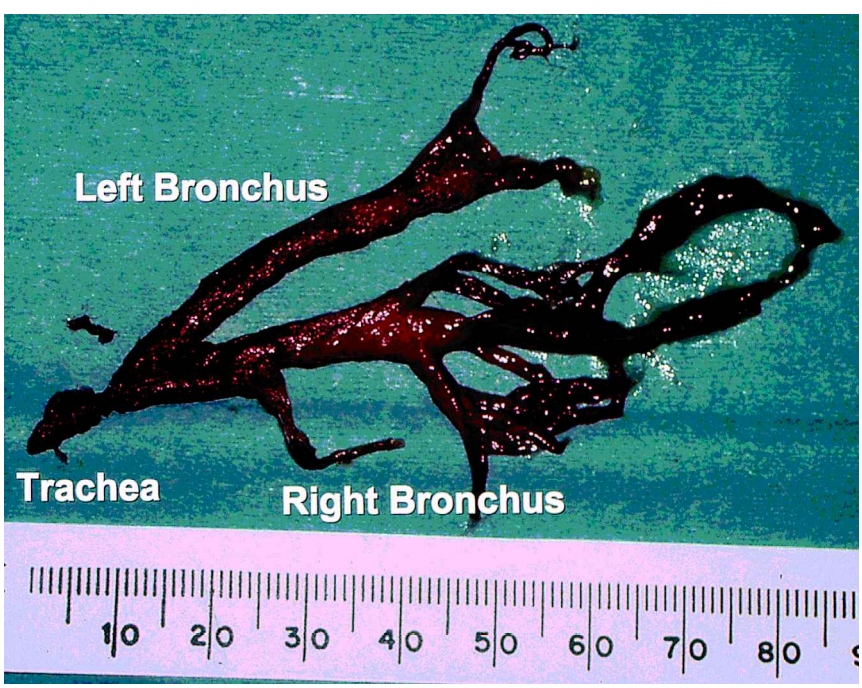

Figure 1.
Cast found within the trachea, occluding both right and left main bronchuses and extending for six bronchial generations. It was removed at bronchoscopy.

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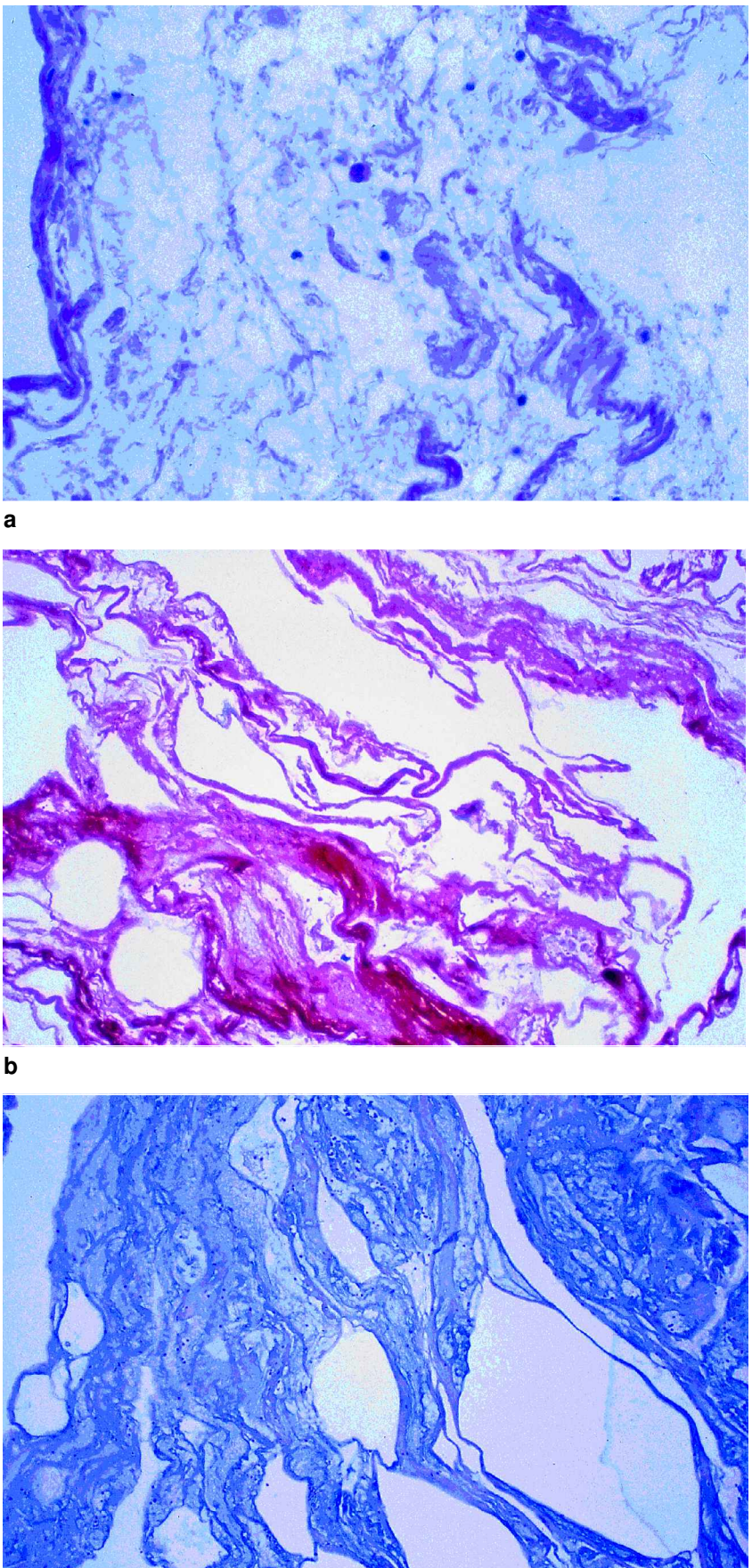

Figure 2.
The cast removed at bronchoscopy (Fig. 2a) is a mixture of fibrin and mucin with very few entrapped cells. Hematoxylin and eosin, original magnification, 100X. Bright red staining of fibrin (Fig. 2b) was revealed with the Trichome stain, original magnification, 25X. The tissue stained prominent blue, indicative of acid mucin (Fig. 2c), when stained with Alcian blue at pH 2.5, original magnification, 25X. The cast retrieved at postmortem examination (Fig. 2d) showed a similar background to that removed at bronchoscopy, but includes far more cells, predominantly a mixture of neutrophils and necrotic epithelial cells.Hematoxylin and eosin, original magnification, 100X. This cast showed a variable amount of bright red staining (Fig. 2e) when processed with the Trichome stain. Original magnification, 100X. Staining with Alcian blue at pH 1.0 (Fig. 2f) revealed very little pale blue staining of neutral mucin. Original magnification 25X.

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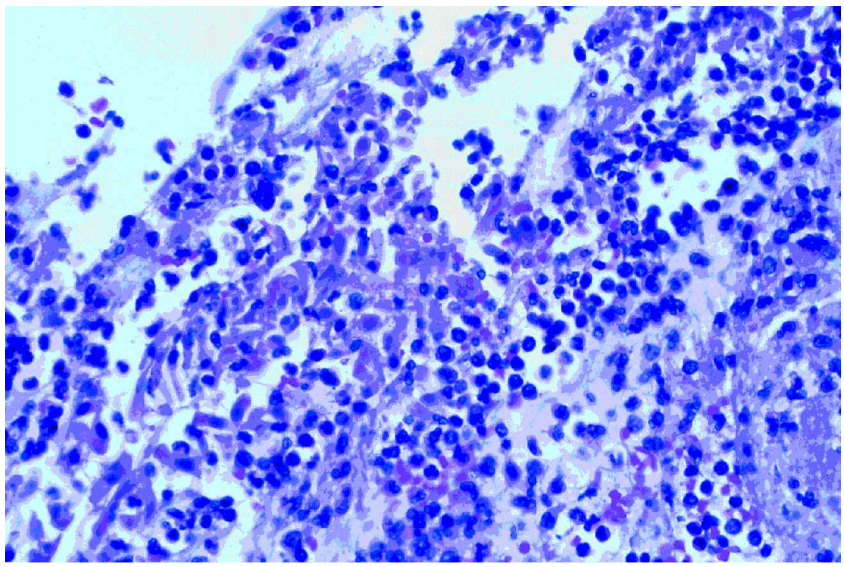

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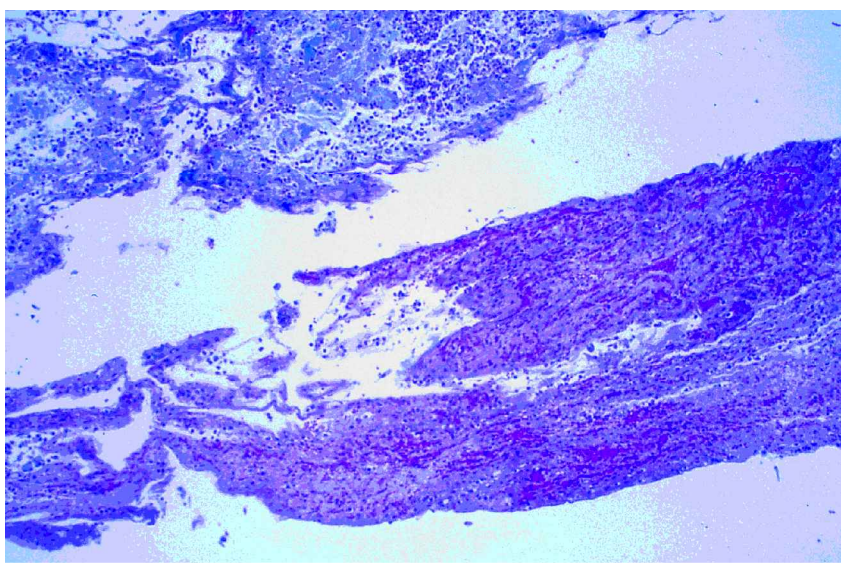

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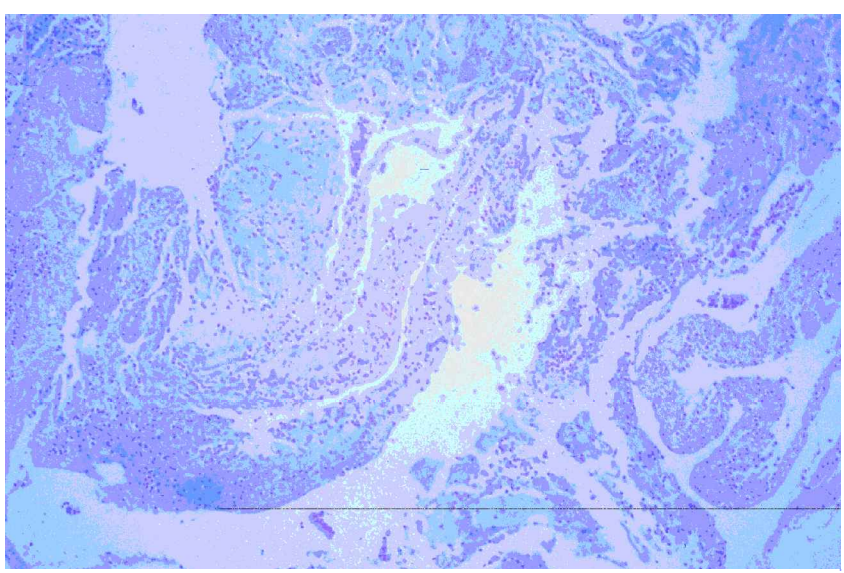

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Cardiac catheterization after the respiratory arrest, 6 months after he began to expectorate casts, and 1 year after creation of the Fontan circuit, demonstrated elevated central venous pressure with two areas of stenosis within the Fontan circuit, specifically at the junction of the right superior caval vein and right pulmonary artery, and between the atrial baffle and right superior caval vein (Table 1). A Palmaz stent (P-188) (Piscataway, New Jersey) was placed in each of these areas producing a reduction in central venous pressure, with mean pressure in the inferior and superior caval veins of 10mmHg (Table 1). This resulted in a transient reduction in production of casts.

Although he produced two casts soon after catheterization, most likely retained prior to procedure, he produced no further casts over a period of six weeks before again being acutely hospitalized. At this time, he had persistent production of casts, with desaturation and respiratory distress, and required inotropic support to maintain adequate cardiac output and intubation and ventilation. Tissue plasminogen activator, in the forms of a 1cc nebulized intravenous formulation, was administered by ultrasonic nebulizer on Servo 300-A (Siemens) in an attempt to degrade the casts, although this did not change saturations, peak airway pressures, or reduce the persistent production. Flexible bronchoscopy revealed a large cast at the carina, which was removed by rigid bronchoscopy. He remained hypoxic and poorly perfused and, despite a second dose of tissue plasminogen activator, he continued to be severely hypoxic and died. Postmortem examination demonstrated multiple casts in the mid-generation airways with distal hyperinflation. The cast material recovered at postmortem examination (Fig. 2d-f) was similar to that seen previously, except for the admixture of numerous cells, predominantly desquamated necrotic respiratory epithelial cells and neutrophils. The stents placed within the Fontan circuit were widely patent with no areas of neointimal build-up.

Postmortem review

A retrospective review was performed of all patients with a Fontan circulation who died at Texas Children's Hospital between January 1989 and June 2000. The postmortem results of 13 patients were reviewed. Although several patients demonstrated nonspecific mucus aggregates within the bronchial tree, there were no patients in whom localized or generalized bronchial casts were observed.

Discussion

The development of plastic bronchitis after the Fontan operation has been well described. Of 14 reported cases of plastic bronchitis in the literature, seven occurred following the creation of a cavo-pulmonary communication.[1,3–5] Seear et al. reviewed one group of 9 patients with plastic bronchitis and classified casts into an inflammatory variant, characterized by a central fibrin mass surrounded by an eosinophil dense infiltrate, and an "acellular" format, characterized by hypocellular material composed of mucin and fibrin with rare mononuclear cells.[1] "Inflammatory casts" are typically seen in association with bronchopulmonary infections, cystic fibrosis, asthma and allergic bronchopulmonary aspergillosis.[6–8] "Acellular" casts are typically associated with cyanotic congenital heart disease in cases with cardiac decompensation, and are typically seen in patients following construction of cavo-pulmonary anastomoses. This production of acellular casts represents a distinct disease entity, and must be differentiated from production of inflammatory cells typical of pulmonary disease. The etiology remains unknown and may be multifactorial. Potential etiologies include elevation of

Table 1. Hemodynamic measurements before and after placement of stents.

Site	6-Month Catheterization*	Post-stent hemodynamics**
Inferior caval vein (mean)	13mmHg	10mmHg
Right superior caval vein	11mmHg	10mmHg
Right pulmonary artery	5mmHg	N/O
Left pulmonary artery	11mmHg	10mmHg

Pressures are expressed as a mean (mmHg).

* Cardiac catheterization six months after the development of recurrent bronchial cast production and one year after completion of the Fontan circulation.

** Catheterization hemodynamics after placement of two stents within the Fontan circuit at the same catheterization. These pressure measurements were following angiography.

Abbreviations: N/O represents value not obtained at catheterization.

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central pulmonary venous pressure,[3] ventricular dysfunction, arrhythmias,[1] and coexistent protein losing enteropathy.[9]

More recent reports suggest alternative pathophysiologies, including abnormalities of endobronchial lymphatic drainage and immune deficiency. Languepin et al. reported a series of three patients with underlying lymphatic abnormalities.[4] These included patients with lipid and lymphocytes in the casts, acquired immune deficiency, and evidence of anatomical lymphatic abnormalities, which they suggested contributed to formation of the casts. One of these patients underwent ligation of the thoracic duct with complete resolution of plastic bronchitis 5 years later. Interestingly, this same patient had evidence of elevated central venous pressure at the time of diagnosis, with a mean inferior caval venous pressure of 11mmHg. No follow-up hemodynamic data was reported.

Although several patients have been reported with casts producted after construction of the Fontan circulation, there is a disconcerting lack of reported hemodynamic data. Our patient is the first to demonstrate a transient reduction in frequency of production of casts coincident with a reduction in the central venous pressure. His mean pulmonary arterial pressure was elevated prior to creation of the Fontan creation, although the pulmonary arteriolar resistance was within normal limits. These features may represent a group of patients predisposed to developing this complication. Despite a reduction in central venous pressure, our patient went on to produce further casts and died from airway obstruction 6 weeks after catheterization. In the series reported by Seear et al., there was a cessation of production of casts after termination of atrial fibrillation in one child with Fontan physiology, and recurrence with further arrhythmia.[1] The same patient had complete cessation subsequent to heart transplantation. This would also infer a relationship between reduction in production of casts and and improved hemodynamics, although the hemodynamic data was not reported in these cases. Interestingly, one of the very first reports of production of casts was in a patient with constrictive pericarditis and cyanotic heart disease, which would further support this hypothesis.[2]

Several attempts have been made in the few reported cases to lyse casts. Several agents, including aerosolized urokinase, tissue-plasminogen-activator, steroids, and clarithromycin, have been attempted as secondary therapies.[10] There are only isolated case reports with each of these therapies, which have proved purely palliative and not altered the course of the disease. Transplantation may be an option, with one previously cited case of resolution following transplantation. Although extracorporeal membrane oxygenation may allow time for extraction of resistant obstructive casts, this would also only be a temporizing measure and not address the underlying etiology.

There is distinctive production of casts seen in patients with a Fontan circulation. This is a unique pathophysiology, and should not be termed plastic bronchitis. The description "Fontan bronchial cast syndrome" would be more appropriate. This complication is rare, occurring in only one patient over the last eleven years at our institution. Hemodynamic evaluation is essential in all patients. Therapies to reduce central venous pressure should be the primary focus before undertaking other measures. Ligation of the thoracic duct does not address this problem. The etiology remains speculative, although ours is the first report of a transient decrease in production of bronchial casts coincident with a reduction in elevated central venous pressure. Unfortunately, this may not be sufficient to significantly alter the natural history of this condition, as in our patient.

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