Pulmonary Function in Long-Term Survivors of Childhood and Adolescence Osteosarcoma: Case Report

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Função Pulmonar em Sobreviventes de Osteossarcoma da Infância e Adolescência: Relato de Caso

Función Pulmonar en Sobrevivientes de Osteosarcoma en la Infancia y la Adolescencia: Relato de Caso

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ABSTRACT

Introduction: Chemotherapy used in osteosarcoma have the potential to cause lung damage. The objectives were to analyze lung volumes and capacities, and respiratory muscle strength of patients treated with chemotherapy and surgery for osteosarcoma. The study was designed as a prospective case-series of patients, through the analysis of spirometry, impulse, oscillometry, and manovacuometry tests. **Case report:** In twenty-one patients, the median age at diagnosis was 15 years, and at inclusion, 30 years. The median disease-free survival time was 10 years. Eight different chemotherapeutic agents were used: cisplatin, doxorubicin, methotrexate, carboplatin, ifophosphamide, epidoxorubicin, cyclophosphamide and etoposide. There were test abnormalities in 14 patients (66.6%), with mild obstructive disorders on spirometry in three patients (14.3%), and obstructive patterns on oscillometry in seven patients (33.3%). On spirometry, the mean ± standard deviation (SD) values of forced vital capacity (FVC) were 91.9%±12.2; for forced expiratory volume in one second (FEV_1) were 87.4%±12.2 and FEV1/FVC ratios, 95.4%±7.9. On oscillometry, mean ± SD values for resistance at 5 Hz were 126.2%±36.2; for resistance at 20 Hz, 128.4%±32.4; reactance at 5 Hz, -0.75±0.68 kPa/L/s; for resonant frequency, 15.6±4.2 Hz. Nine patients (42.8%) had reduced maximum pressures on the manovacuometry: Maximum Expiratory Pressure (MEP) were reduced in eight patients, and inspiratory (MIP) in three. The mean ± SD MIP was 89.4±29.5; MEP, 88±37.7. **Conclusion:** Mild abnormalities in pulmonary function tests in this series of patients were observed years after treatment for osteosarcoma.

Key words: Osteosarcoma; Lung Volume Measurements; Spirometry; Oscillometry; Antineoplastic Agents.

RESUMO

Introdução: A quimioterapia usada no osteossarcoma tem potencial para causar danos aos pulmões. Os objetivos deste trabalho foram analisar os volumes e capacidades pulmonares e a força respiratória de pacientes tratados com quimioterapia e cirurgia para osteossarcoma, em uma série prospectiva de casos, em um hospital pediátrico oncológico, por meio da análise de espirometria, oscilometria de impulso e manovacuometria. **Relato de caso:** Em 21 pacientes, a mediana de idade ao diagnóstico foi de 15 anos e na inclusão de 30 anos. O tempo médio de sobrevida livre de doença foi de dez anos. Houve alterações nos exames em 14 pacientes (66,6%), com distúrbios obstrutivos leves na espirometria em três pacientes (14,3%) e padrões obstrutivos na oscilometria em sete pacientes (33,3%). Na espirometria, os valores de média ± desvio padrão (DP) da capacidade vital forçada (CVF) foram 91,9%±12,2; para o volume expiratório forçado no primeiro segundo (VEF1) foram 87,4%±12,2 e as relações VEF1/CVF, 95,4%±7,9. Na oscilometria, os valores médios ± DP para resistência em 5 Hz foram 126,2%±36,2; para resistência a 20 Hz, 128,4% ± 32,4; reatância a 5 Hz, -0,75 ± 0,68 kPa/L/s; para frequência de ressonância, 15,6±4,2 Hz. Na manovacuometria, nove pacientes (42,8%) apresentaram redução nas pressões: as pressões expiratórias máximas (PEmáx) foram reduzidas em oito pacientes e as inspiratórias (PImáx) em três. A média ± DP da PImáx foi 89,4±29,5; PEmáx, 88±37,7. **Conclusão:** Observaram-se alterações leves nos testes de função pulmonar anos após o tratamento do osteossarcoma.

Palavras-chave: Osteossarcoma; Medidas de Volume Pulmonar; Espirometria; Oscilometria; Antineoplásicos.

RESUMEN

Introducción: La quimioterapia utilizada en osteosarcoma puede causar daño a los pulmones. Los objetivos de este trabajo fueron analizar los volúmenes y capacidades pulmonares y la fuerza respiratoria en pacientes tratados para osteosarcoma, en una serie prospectiva de casos, en un hospital de oncología pediátrica, mediante el análisis de espirometría, oscilometría de impulsos y manuvacuometría. **Relato de caso:** En 21 pacientes, la mediana de edad al diagnóstico fue de 15 años y en la inclusión de 30 años. La supervivência media libre de enfermedad fue de diez años. Hubo alteraciones en los exámenes en 14 pacientes (66,6%), con alteraciones obstructivas leves en la espirometría en tres (14,3%), y obstrucción en la oscilometría en siete (33,3%). En espirometría, las medias ± desviación estándar (DE) de la capacidad vital forzada (CVF) fueron 91,9%±12,2; para el volumen espiratorio forzado en el primer segundo (VEF1) fue 87,4%±12,2 y el cociente VEF1/CVF fue 95,4%±7,9. En oscilometría, los valores medios ± DE para la resistencia a 5 Hz fueron 126,2%±36,2; para resistencia a 20 Hz, 128,4%±32,4; reactancia a 5 Hz, -0,75±0,68 kPa/L/s; para la frecuencia de resonancia, 15,6±4,2 Hz. En manuvacuometría, nueve pacientes (42,8%) mostraron una reducción de las presiones: las presiones espiratorias máximas (PEmáx) se redujeron en ocho pacientes y las presiones inspiratorias (PImáx) en tres. La media ± DE del PImáx fue 89,4 ± 29,5; PEmáx, 88±37,7. **Conclusión:** Se observaron ligeros cambios en las pruebas de función pulmonar años después del tratamiento del osteosarcoma.

Palabras clave: Osteosarcoma; Mediciones del Volumen Pulmonar; Espirometría; Oscilometría; Antineoplásicos.

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INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor in children, adolescents, and young adults, most frequently affecting the metaphysis of long bones[1]. At the diagnosis, 10 to 20% of the patients have pulmonary metastases, and subsequently, in nearly 50% of the patients, they can occur even during treatment[2] leading to segmentectomy or lobectomy. Chemotherapy treatment usually uses high doses of methotrexate, associated with cisplatin and doxorubicin, among other agents[3]. Methotrexate provokes, in addition to other side effects, pulmonary toxicity, which can cause pneumonitis, and in some cases, the reduction of ventilatory capacity for months after discontinuation[4,5]. Long-term changes in lung function have been reported for other chemotherapeutic agents such as cisplatin[6].

This study aimed to analyze lung volumes and capacities, in addition to respiratory muscle strength in patients who underwent chemotherapy and surgical treatment for osteosarcoma, associated or not with thoracotomies for resection of lung metastases.

The study was carried out from January to April 2017 at the Pediatric Oncology Institute - Support Group for Adolescents and Children with Cancer (IOP-GRAACC), in partnership with the Clinic of Allergy, Immunology and Rheumatology of the Department of Pediatrics at the Federal University of São Paulo (UNIFESP), where the exams were performed by skilled technicians and after daily calibration of the devices. The Institutional Review Board approved the protocol (CAAE: 60554716.0.0000.5505). Patients diagnosed with osteosarcoma with at least 2-years disease-free survival time without respiratory infection, and who consented by signing the Informed Consent Form were included.

METHOD

Impulse Oscillometry was performed with a MasterScreen™ equipment (CareFusion, USA). The measurement of the elastic and resistive components was conducted during normal current breathing, with manual support of the cheeks and use of a nose clip. At least three technically acceptable tests were completed, with a minimum duration of 30 seconds. The average values of the following parameters were recorded: resistance at 5 Hertz (R5) representing the total airway resistance; resistance to 20 Hertz, representing the central resistance of the airways (R20); reactance at 5 Hertz (X5) representing the peripheral elastic properties; resonant frequency (Fres), representing the point where the inertial and elastic forces reach the same magnitude. Resistance values at 5 Hz or 20 Hz ≥ 150% of the predicted values, reactance at 5 Hz if X5 < (predicted X5 - 0.2 kPa/L/s) and resonant frequency >12 Hz were considered out of normal[7,8].

Spirometry was also performed on a certified MasterScreen™ equipment (CareFusion - USA). Patients were instructed to perform a maximum inspiration until the total lung capacity, followed by forced expiration with vigorous stimulation, so that the effort was the maximum at the beginning of the maneuver and prolonged until the residual volume, in a mouthpiece, with the lips closed in order to avoid leaks, with a minimum duration of three seconds and a plateau of at least one second. The measurements were repeated until three values technically acceptable were obtained, being two reproducible. The values of FEV_1 (forced expiratory volume in one second), FVC (forced vital capacity), FEV_1/FVC ratio <80% of the predicted and Forced Mid-Expiratory Flow ($FEF_{25-75\%}$) rates <65% (under 18 years old) of the predicted values were considered out of the normal range. The classification of the obstructive ventilatory disorder was in accordance with the criteria of the pulmonary function consensus of the American Thoracic Society in conjunction with the European Society of Pulmonology (ATS/ ERS)[9,10].

Manovacuometry was performed with a calibrated equipment, with variation of ± 120 cmH2O, (Comercial Medica model M120). Tests were performed with the patients seated, using a nasal clip and a mouthpiece with an orifice of approximately 2 mm in diameter to avoid the increase of intraoral pressure during the maneuvers. To measure the MIP (Maximum Inspiratory Pressure), patients were instructed to perform three normal current breaths; on the third current breath, perform a forced expiration until the residual volume, followed by a maximum inspiration until the total lung capacity, sustained for a second. The same procedure was used to measure MEP (Maximum Expiratory Pressure), with a maximum forced expiration up to the residual volume, sustained for one second. The measurements were repeated until three values technically acceptable and reproducible were obtained. The highest value was considered for analysis, provided that the second highest value was not exceeded by 10%. For the determination of reference values for each age group, mean values ± (1.96 × standard deviation) were used, as reported by Cosa et al.[11] for patients older than 18 years of age, and by Hulzebos et al.[12] for patients under 18 years.

CASE REPORT

Twenty-one patients were enrolled. None of them has been submitted to respiratory evaluation before.

The median age at diagnosis was 15 years (interquartile range - IQR 25-75: 11-20.5 years). The median disease-free survival time was 10 years (IQR 5.5-17.5), and the median age at inclusion was 30 years (IQR 17-36). The primary tumor location was the femur in 10 cases, tibia in four cases, fibula in one case and humerus in six cases. All patients underwent orthopedic surgery for local tumor control and chemotherapy, and seven patients underwent lung surgery. Eight different chemotherapeutic agents were used: cisplatin, doxorubicin, methotrexate, carboplatin, ifophosphamide, epidoxorubicin, cyclophosphamide and etoposide. The cases are summarized in Table 1, which shows the chemotherapy protocols, pulmonary surgical interventions and abnormalities observed in the tests of 14 patients (seven patients have had all tests normal). Mild obstructive disorders were observed on spirometry in three patients (14.3%), and restrictive pattern was observed in two patients (9.5%); on impulse oscillometry, distal obstruction disorders were present in seven patients (33.3%), and restriction in two patients (9.5%).

The mean ± SD (standard deviation) values of FVC were 91.9% ± 12.2; for FEV1, were 87.4% ± 12.2, and for FEV1/FVC ratio, 95.4% ± 7.9. In oscillometry, mean ± SD values for resistance at 5 Hz were 126.2% ± 36.2; for resistance at 20 Hz, 128.4% ± 32.4; reactance at 5 Hz, -0.75 ± 0.68 kPa/L/s; for resonant frequency, 15.6 ± 4.2 Hz. These results are presented in Figure 1.

Nine patients (42.8%) had reduced maximum pressures on the manovacuometry: MEP was reduced in seven patients and MIP in three. The mean ± SD MIP were 89.4 ± 29.5; MEP, 88 ± 37.7. Out of these nine patients, four were the only ones in the sample with a respiratory complaint of dyspnea when climbing stairs.

Table 1. Data on patient characteristics and abnormalities observed in the tests

	Age (years), sex, BMI	Protocol	Pulmonary surgery due to metastasis	Disease-free survival time (years)	Abnormalities observed in the tests, disorder classification by spirometry (S) and oscillometry (O)
1	19, female. BMI 18.8	GLATO 2006*	None	3	⇓ MEP (40cmH2O)
2	14, female. BMI 22	GLATO 2006*	None	6	⇓ MEP (48 cmH_2O) S: mild obstruction/O: distal obstruction
3	31, female. BMI 21.8	GLATO 2006*	1 (nodule resection)	9	⇓ MEP (45 cmH2O) S: mild restriction
4	26, male. BMI 27.5	GLATO 2006	2 (nodule resection)	8	⇓ MEP (60 cmH2O) S: mild obstruction/O: distal obstruction
5	17, male. BMI 22.7	GLATO 2006*	1 (lobectomy)	2	O: distal obstruction
6	23, male. BMI 21	GLATO 2006*	1 (nodule resection)	9	S: restriction/ O: restriction
7	38, female. BMI 41.3	Ifophosphamide, carboplatin, doxorubicin, and cisplatin	None	18	O: distal obstruction
8	36, male. BMI 36.6	Epidoxorubicin, Ifophosphamide, carboplatin	None	23	⇓ MIP (90 cmH2O) O: distal obstruction
9	37, female BMI 25	Epidoxorubicin, Ifophosphamide, carboplatin, methotrexate	None	20	⇓ MEP (45 cmH2O)

to be continued

Table 1. continuation

	Age (years), sex, BMI	Protocol	Pulmonary surgery due to metastasis	Disease-free survival time (years)	Abnormalities observed in the tests, disorder classification by spirometry (S) and oscillometry (O)
10	32, male. BMI 23.8	Ifophosphamide, doxorubicin, cisplatin	None	16	⇓ MEP (60 cmH2O) ⇓ MIP (60 cmH2O)
11	42, female. BMI 22.3	Ifophosphamide, doxorubicin, carboplatin, and cisplatin	None	18	⇓ MEP (40 cmH2O) ⇓ MIP (20 cmH2O) S: mild obstruction
12	35, female BMI 32.4	Ifophosphamide, doxorubicin, cisplatin	None	13	⇑ reactance at 5 Hz (-1.07), ⇑ resonant frequency (17.5): restriction ⇓ MEP (40 cmH2O)
13	40, male. BMI 38.3	Ifophosphamide, doxorubicin, carboplatin, etoposide	None	25	O: distal obstruction
14	36, male BMI 33.3	Ifophosphamide, doxorubicin, cyclophosphamide, and cisplatin	2 (nodule resection)	15	O: distal obstruction

Captions: BMI = Body Mass Index.
(*) GLATO 2006, a protocol of the Latin American Osteosarcoma Treatment Group, with high dose methotrexate, cisplatin, and doxorubicin[13].

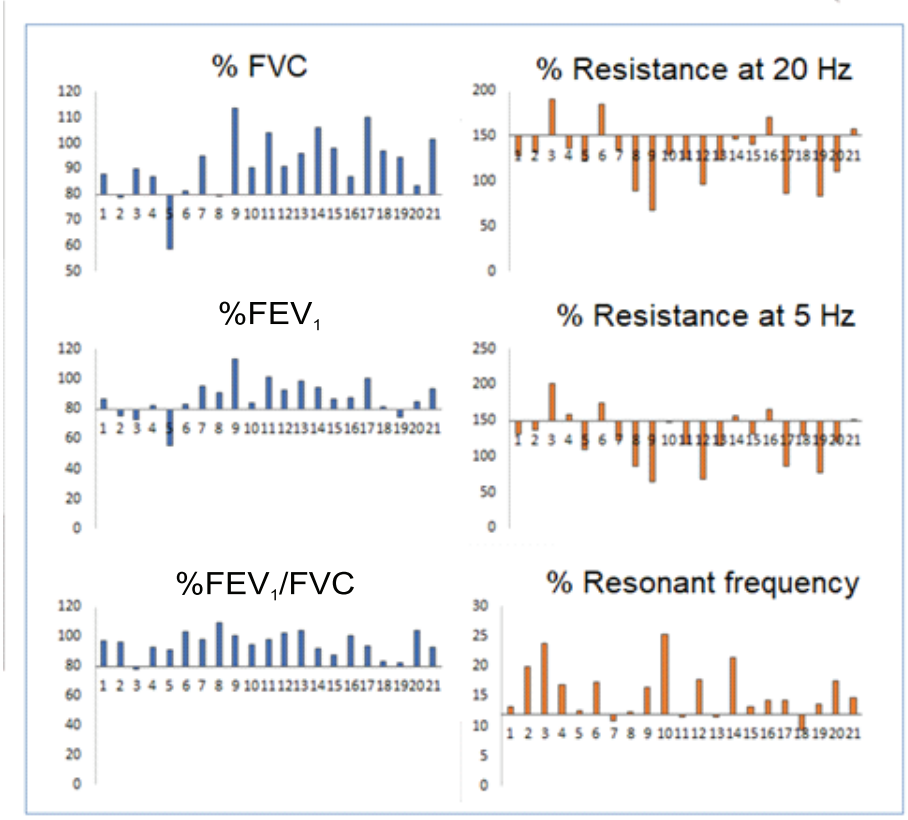

Figure 1. Values of FVC (forced vital capacity), FEV_1 (forced expiratory volume in one second), FEV_1/FVC ratios, resistance values at 5 and 20 Hz and resonant frequency. The X axes of the graphs cut the Y axis at the defined cutoff values

DISCUSSION

In this series of cases, mild obstructive disorders on spirometry in three patients were observed. Only one has a history of pulmonary metastasectomy. Two patients presented restrictive patterns, and both suffered a pulmonary metastasectomy. Spirometric changes after pulmonary metastasectomy are determined by the volume of resected parenchyma, and functional loss after three or more non-anatomical resections is comparable with that recorded after lobectomy[14]. In common, the patients with mild obstructive disorders received chemotherapy protocols based on cisplatin. Cisplatin can cause an acute decline in alveolo-capillary membrane diffusing capacity, which is usually subclinical[15]. Impaired pulmonary function has been reported after more than 20 years after survivors of testicular cancer were treated with cisplatin-based chemotherapy[16]. Due to the nature of the present study, however, it is not possible to establish cause and effect relationships, or even correlations, between the drugs used and the abnormalities observed in the exams.

On impulse oscillometry, distal obstructive patterns in seven patients of the sample were observed, with increases in resistance, and restrictive patterns in two patients. Airway resistance from low frequency to high frequency reflects the airway resistance change from peripheral to central tissues. Elevated resonant frequency was a frequent finding but cannot be attributed to a specific mechanical property of the lungs. In lung diseases, both obstructive and restrictive, it is increased above normal, because of reactance becoming more negative at low frequencies in each of these conditions[8]. In cancer patients, impulse oscillometry could be useful to measure the mechanics of the respiratory system because it is simple, fast, non-invasive, and does not require forced maneuvers that could influence bronchial tone. Spirometry requires active patient cooperation and therefore, may be difficult for some patients to exert, particularly in postoperative period[17].

Manovacuometry is a simple way to measure maximum respiratory pressures, generating a quantitative assessment of the function and strength of respiratory muscles[11]. Abnormalities in maximum respiratory pressures in 9 patients were observed, suggesting impaired respiratory muscle strength.

This study was carried out in a single referral center for pediatric cancer treatment in Brazil. The difficulty in recruiting patients already out of treatment for an outpatient evaluation precluded the possibility of a greater sample and statistical analysis of subgroups. However, it was possible to show the presence of multiple changes in lung function, although in many cases mild, for most of the patients evaluated. This fact demonstrates the need for systematic assessment of lung function in the short and long term in cancer patients undergoing aggressive chemotherapy, particularly osteosarcoma.

CONCLUSION

Even several years after treatment, mild changes in lung function in patients who received treatment for osteosarcoma in childhood and adolescence were encountered.

CONTRIBUTIONS

All authors contributed equally to the design and planning of the study, collection, analysis and interpretation of the data, wording, critical review and approved the final version to be published.

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DECLARATION OF CONFLICT OF INTEREST

There is no conflict of interest to declare.

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REFERENCES

1. Eleutério SJP, Senerchia AA, Almeida MT, et al. Osteosarcoma in patients younger than 12 years old without metastases have similar prognosis as adolescent and young adults. Pediatr Blood Cancer. 2015;62(7):1209-13. doi: https://doi.org/10.1002/pbc.25459
2. Farfalli GL, Albergo JI, Lobos PA, et al. Metástasis pulmonares en osteosarcoma neoadyuvancia, tratamiento quirúrgico y supervivencia. Medicina (B Aires). 2015;75(2):87-90.
3. Picci P, Mercuri M, Ferrari S, et al. Survival in high-grade osteosarcoma: improvement over 21 years at a single institution. Ann Oncol. 2010;21(6):1366-73. doi: https://doi.org/10.1093/annonc/mdp502
4. Imokawa S, Colby TV, Leslie KO, et al. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J. 2000;15(2):373-81. doi: https://doi.org/10.1034/j.1399-3003.2000.15b25.x
5. Lateef O, Shakoor N, Balk RA. Methotrexate pulmonary toxicity. Expert Opin Drug Saf. 2005;4(4):723-30. doi: https://doi.org/10.1517/14740338.4.4.723

6. Haugnes HS, Oldenburg J, Bremnes RM. Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors. Urol Oncol. 2015;33(9):399-406. doi: https://doi.org/10.1016/j.urolonc.2014.11.012
7. Valle ELT. Resistência das vias aéreas: técnica da oscilação forçada. J Pneumol. 2002;28(Suppl 3):S151-S154.
8. Desiraju K, Agrawal A. Impulse oscillometry: the state-of-art for lung function testing. Lung India. 2016;33(4):410-6. doi: https://doi.org/10.4103/0970-2113.184875
9. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. doi: https://doi.org/10.1183/09031936.05.00034805
10. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68. doi: https://doi.org/10.1183/09031936.05.00035205
11. Cosa D, Gonçalves HA, Lima LP, et al. Novos valores de referência para pressões respiratórias máximas na população brasileira. J Bras Pneumol. 2010;36(5):306-312. doi: https://doi.org/10.1590/S1806-37132010000500021
12. Hulzebos E, Takken T, Reijneveld EA, et al. Reference values for respiratory muscle strength in children and adolescents. Respiration. 2018;95(4):235-3. doi: https://doi.org/10.1159/000485464
13. Petrilli AS, de Camargo B, Odone Filho V, et al. Results of the Brazilian Osteosarcoma Treatment Group Studies III and IV: prognostic factors and impact on survival. J Clin Oncol. 2006;24(7):1161-8. doi: https://doi.org/10.1200/JCO.2005.03.5352
14. Petrella F, Chieco P, Solli P, et al. Which factors affect pulmonary function after lung metastasectomy? Eur J Cardiothorac Surg. 2009;35(5):792-6. doi: https://doi.org/10.1016/j.ejcts.2009.01.011
15. Leo F, Solli P, Spaggiari L, et al. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? Ann Thorac Surg. 2004;77(1):260-5. doi: https://doi.org/10.1016/s0003-4975(03)01487-5
16. Stelwagen J, Lubberts S, Steggink LC, et al. Vascular damage and pulmonary function in very long-term survivors of testicular cancer (TC) treated with cisplatin-based chemotherapy. Ann Oncol. 2018;29(Suppl 8):viii324. doi: https://doi.org/10.1093/annonc/mdy283.120
17. Jara-Gutierrez P, Aguado E, Del Potro MG, et al. Comparison of impulse oscillometry and spirometry for detection of airway hyperresponsiveness to methacholine, mannitol, and eucapnic voluntary hyperventilation in children. Pediatr Pulmonol. 2019;54(8):1162-72. doi: https://doi.org/10.1002/ppul.24409

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