Caso clínico

Hyperthermic Intrathoracic Chemotherapy: A new weapon has been deployed in Portugal

Quimioterapia Intratorácica Hipertérmica: Uma nova arma em Portugal

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Abstract

Thymoma is a relatively rare tumour, being, nonetheless, the most frequent neoplasm of the anterior mediastinum. Radical surgery is the gold-standard in every stage, with a considerable recurrence rate in locally advanced tumours. Complete resection in recurrences occurs only in a few cases. A new therapeutic strategy has emerged: the Hyperthermic Intrathoracic Chemotherapy (HITHOC), a high concentrated dose of chemotherapy applied locally, that has been used in addition to radical surgery to improve local control of pleural metastasis and other pleural tumours. We report a case of a 42-year-old woman diagnosed with Masaoka-Koga stage III thymoma, who underwent radical surgery, and later had a recurrence presenting with pleural metastasis. The patient underwent surgical resection followed by HITHOC, with success. HITHOC is proven to be safe and effective, but has not yet been widely used. To our knowledge, this was the first time that HITHOC has been implemented in Portugal.

Key-words: *Hyperthermic Intrathoracic Chemotherapy (HITHOC); Thymoma; Intracavitary chemotherapy.*

Resumo

O timoma é um tumor relativamente raro, sendo, no entanto, a neoplasia mais frequente do mediastino anterior. A cirurgia radical é o *gold-standard* em todos os estadios, apresentando uma taxa de recorrência considerável em tumores localmente avançados, cuja ressecção completa ocorre apenas em alguns casos. Uma nova estratégia terapêutica tem vindo a ser desenvolvida: a Quimioterapia Intratorácica Hipertérmica (HITHOC), uma alta dose concentrada de quimioterapia aplicada localmente, em associação com a cirurgia radical, para melhorar o controlo local de metástases pleurais. Relatamos o caso de uma mulher de 42 anos com diagnóstico de timoma estadio III de Masaoka-Koga, submetida a cirurgia radical, que apresentou recidiva com metastização pleural. A doente foi submetida a ressecção cirúrgica seguida de HITHOC, com sucesso. A HITHOC é uma terapêutica segura e eficaz, mas ainda não é amplamente utilizada. Do nosso conhecimento, esta foi a primeira vez que a HITHOC foi realizada em Portugal.

Palavras-chave: Quimioterapia Intratorácica Hipertérmica (HITHOC); Timoma; Quimioterapia intracavitária.

Introduction

Thymoma is a relatively rare tumour that arises from the epithelial cells of the thymus. Although rare, it is the most frequent neoplasm of the anterior mediastinum. Complete surgical resection plays a fundamental role in the management of thymomas, even in advanced stage. In such cases, recurrences can occur up to 30% of after radical resection, with pleura and pericardium representing the most frequent sites.[1] In most cases of stage IVA Masaoka-Koga, radical surgery is recommended for better local control of disease or paraneoplastic syndromes. However, the reports show that complete resection is achieved in less than two-thirds of cases, leading to poorer prognosis.[2]

In this scenario, new therapeutic strategies have been emerging, as Hyperthermic Intrathoracic Chemotherapy (HITHOC), a high concentrated dose of warmed chemotherapy, introduced and circulated in the thorax. HITHOC has been used in addition to radical surgery to improve local control of tumours such as mesothelioma, pleural metastasis from thymoma, thymic carcinoma and occasionally from lung and ovary cancer.[3] The use of HITHOC for this purpose has been reported for several years already, but recently, there has been a growing interest in this procedure.

In this report, we present a clinical case of the use of HITHOC as adjuvant of surgery for the treatment of pleural thymoma metastasis.

Case report

A 42-year-old woman diagnosed with Masaoka-Koga stage III B1 thymoma, pT3pN0cM0 – TNM stage IIIA, with right superior pulmonary lobe, superior vena cava, innominate vein and pericardium invasion, and Good's syndrome in 2018. The patient underwent radical *en bloc* surgical resection, with phrenic nerve preservation and superior vena cava reconstruction using autologous pericardium patch. The pathology report revealed a complete macroscopic resection with focal microscopic invasion of the surgical margins (R1).

The patient underwent postoperative radiotherapy between february and april 2019, at a total dose of 54 Gy in 27 fractions. Gammaglobulin replacement 40mg every 3 weeks was also conducted, with clinical improvement.

In 2020, a follow-up chest computed tomography (CT) scan revealed a 7 cm pleural mass located in the posterior costophrenic recess (**Fig. 1**). An ultrasound-guided transthoracic biopsy was subsequently conducted, confirming the presence of a thymoma metastasis and staging it as a Masaoka-Kiga stage IVA Thymoma. Following the diagnosis, the patient underwent chemotherapy treatment with cyclophosphamide (500mg/m² iv), doxorubicin (50mg/m² iv) and cisplatin (50mg/m² iv), administered every 21 days. After completing six cycles, a re-evaluation CT in September 2021 inidicated

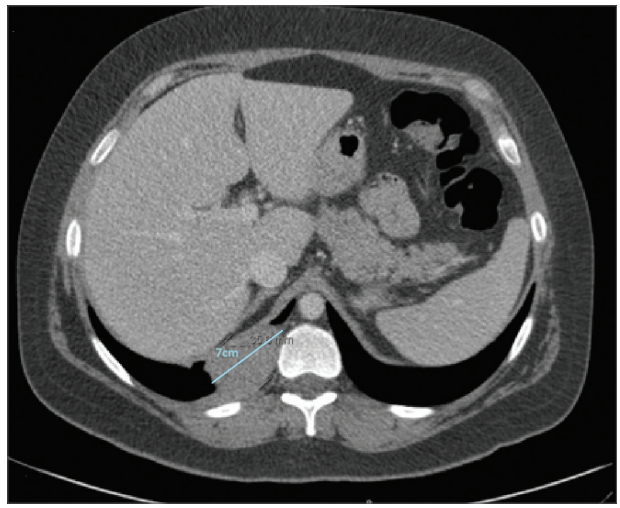

Figure 1. Chest computed tomography showing a 7cm pleural mass in the right posterior costophrenic recess.

disease stability. In a multidisciplinary discussion, the decision was made to proceed with surgical resection followed by HITHOC (Hyperthermic Intrathoracic Chemotherapy). A specific protocol for the HITHOC procedure was developed, guided by recommendation from the international literature.[4-7]

Single port-video-assisted thoracoscopic surgery was performed under general anaesthesia, with single lung ventilation, using a lateral position. The procedure involved the complete macroscopic resection of a large thymoma metastasis, measuring 10,5x7x5,5cm (**Fig. 2**). Subsequent anatomopathological examination confirmed a R0 resection.

Following the resection, the patient was repositioned with a closed thorax, in the supine position for HITHOC. To perform HITHOC, we used a LivaNova S5® heart-lung machine. The pleural space was progressively filled with the preloaded Hemosol B0® (a solution consisting of a mixture of the following five active ingredients: calcium chloride dihydrate, magnesium chloride hexahydrate, (S)-lactic acid, sodium bicarbonate and sodium chloride). Two 32-French (32-F) chest tubes

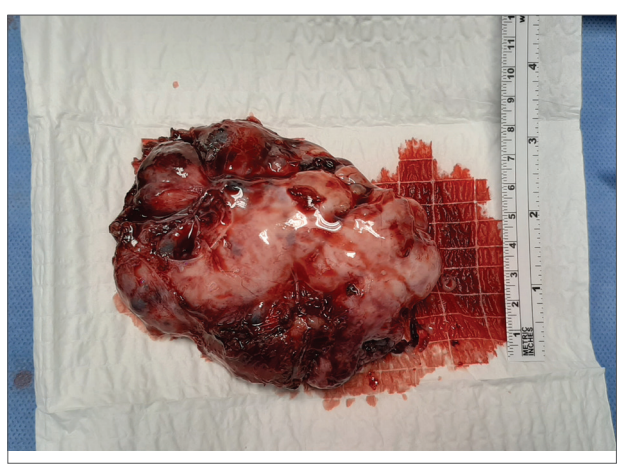

Figure 2. Resected thymoma metastasis (185g, 10,5x7x5,5cm).

were placed accordingly (apical inflow and basal outflow drains), ensuring circulation throughout the entire pleural space. The solution temperature was progressively increased up to 42°C (minimum temperature of 39,5ºC; mean temperature of 40ºC). The chemotherapeutic agent used was cisplatin at a dose of 150 mg/m², and was added to the solution when the temperature stabilised. The infusion was carried out for sixty minutes at a flow of 1500 mL/min (**Fig. 3**). Pre- and postoperative hydration (including 500mL of Ringer Lactate and a total of 4700 mL of Polyelectrolyte solution without dextrose), and forced diuresis were performed to prevent cisplatin-induced kidney injury. The intra- and postoperative periods were uneventful. The patient stayed in the intensive care unit for 2 days, and was discharged five days after the procedure. Likewise, no complications were reported in the late postoperative period related to HITHOC. Chest CT at 3 and 12 months of follow-up excluded disease recurrence. The patient remains assimptomatic and maintains regular clinical and radiological follow-up at the Oncology Clinics.

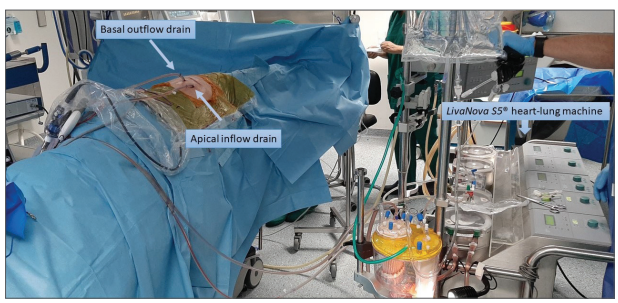

Figure 3. Hyperthermic intrathoracic chemotherapy procedure using a LivaNova S5® heart-lung machine and two 32F drains.

Discussion

Locally advanced thymomas are characterised by a high rate of pleural and pericardial relapses. Surgical resection remains pivotal in thymoma management, even in advanced stages, often as a part of multimodal strategy. This involves chemotherapy and radiotherapy combined or alone, and more recently HITHOC.[4] This technique relies on three key factors that enhance the synergy between hyperthermia and some cytotoxic drugs: increased membrane permeability of the targeted tissues, enhanced cytotoxicity by changing drug pharmacokinetics, and improved drug penetration into tissues in a temperature-dependent manner. Local administration of the chemotherapeutic agent allows greater drug concentration in the targeted tissue, minimizing systemic toxicities. Cisplatin's median penetration depth of 3–4 mm is encouraging, given that the treatment targets residual malignant cells.[5,8,9]

HITHOC is performed using a pump and a heat exchanger, connected to inflow and outflow chest tubes to allow unidirectional perfusion, thus avoiding recirculation. This is continued for 60-90 min at a targeted temperature of 38-43ºC. The amount of perfusate varies from 1500 to 3500 mL according to body surface square metres.[2-5,9] Cisplatin is the most commonly used cytostatic agent with the most reported evidence in HITHOC. Therefore, cisplatin plays the major role for the chemotherapeutic perfusion, given at a dosage between 150-175 mg/m². Cisplatin may also be used in combination with other cytostatic drug such as doxorubicin, mitomycin, epirubicin, adriamycin or gemcitabine. However, the therapeutic benefit and the optimal dosage of the second cytostatic drug remain unclear, hence our decision to choose cisplatin as monotherapy Both, the dosage of cisplatin and the amount of perfusion fluid, are essential to establish a high intrathoracic concentration of cisplatin.[5,8,9]

The most common complications associated with the procedure are renal insufficiency, intraoperative arrhythmias, empyema, thrombocytopenia and bleeding, with an overall incidence of 2%. Furthermore, postoperative morbidity and mortality are mainly caused by the surgical cytoreduction itself and not primarily by HITHOC.[5,6,8,9]

HITHOC treatment has not yet been widely used but it has been proven to be effective and safe in the treatment of primary and secondary malignant pleural tumours.[4,5] There is no standardised protocol for HITHOC. It has been described that HITHOC has a significant impact on extending the median survival and one to five-year survival rates, particularly in patients with thymoma, even when considering the indolent nature of these tumours. Maury et al. reported a median OS was 63 months and 1- and 5-year survival rates were 93% and 86%, respectively.[10] Nevertheless, prospective studies are strongly required.

To our knowledge, this is the first application of HITHOC in Portugal and in this regard, we hope to prospectively evaluate and implement it as a standardised procedure in our centres, permiting more individualized treatments.

Contributorship Statement / Declaração de Contribuição

R. Ferreira was the head surgeon.

B. Drayblate was the second surgeon.

F. Pereira was the perfusionist in the HITHOC procedure.

R. Ferreira and E. Brysch, C. Barata, participated in protocol creation.

C. Barata and R. Ferreira were responsible for drafting of the manuscript.

R. Ferreira, E. Brysch and A. Nobre were responsible for critical revision of the manuscript for important intellectual content.

R. Ferreira foi o cirurgião principal.

B. Drayblate foi o segundo cirurgião.

F. Pereira foi o perfusionista no procedimento HITHOC.

R. Ferreira e E. Brysch, C. Barata, participaram da criação do protocolo.

C. Barata e R. Ferreira foram responsáveis pela elaboração do manuscrito.

R. Ferreira, E. Brysch e A. Nobre foram responsáveis pela revisão crítica do manuscrito quanto ao conteúdo intelectual.

Ethical Disclosures / Responsabilidades Éticas

Protection of humans and animals: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

Data confidentiality: The authors declare having followed the protocols in use at their working center regarding patients' data publication.

Patient consente: Obtained.

Competing interests: The authors have declared that no competing interests exist.

Fundings: There were no external fundings.

Proteção de humanos e animais: Os autores declaram que os procedimentos foram seguidos de acordo com os regulamentos estabelecidos pelo Comitê de Pesquisa Clínica e Ética e com a Declaração de Helsinque da Associação Médica Mundial.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos em uso em seu centro de trabalho em relação à publicação de dados de pacientes.

Consentimento do paciente: Obtido.

Conflito de interesses: Os autores declararam que não há conflito de interesses.

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