Malignant pleural mesothelioma in a child: long-term survival with ICE-WAC chemotherapy regimen

Kamer Mutafoğlu-Uysal[1], Aydanur Kargı[2], Faik Sarıalioğlu[1]
Nur Olgun[1], Arzu Kovanlıkaya[3]

[1]Department of Pediatric Oncology, Institute of Oncology, and Departments of [2]Pathology, and [3]Radiology, Dokuz Eylül University, Faculty of Medicine, İzmir, Turkey

SUMMARY: Mutafoğlu-Uysal K, Kargı A, Sarıalioğlu F, Olgun N, Kovanlıkaya A. Malignant pleural mesothelioma in a child: long-term survival with ICE-WAC chemotherapy regimen. Turk J Pediatr 2002; 44: 244-247.

Malignant mesothelioma is a very rare tumor in childhood. Presently, treatment of this disease continues to be frustrating and prognosis remains poor. We here report a pediatric case of malignant pleural mesothelioma who gave a complete response to ICE-VAC chemotherapy regimen and achieved a long-term survival. An eight-year-old girl underwent exploratory thoracotomy and decortication because of a unilateral loculated and multicystic pleural effusion. Histopathological diagnosis was sarcomatoid pleural malignant mesothelioma. After decortication, chemotherapy with ICE (ifosfamide, carboplatin, etoposide) - VAC (vincristine, adriamycin, cyclophosphamide) combination was started. Six courses of chemotherapy resulted in complete clinical and radiological tumor response. She did not receive any further therapy and remains disease-free three years after the first remission. ICE-VAC chemotherapy combination resulted in a complete tumor response and a long-term disease-free survival for the presented case. The efficacy of this chemotherapy regimen in malignant mesothelioma needs to be documented in future trials.

Key words: malignant mesothelioma, ICE, ICE-VAC, chemotherapy, rare tumors.

Malignant mesothelioma (MM) is a very rare tumor of childhood, accounting for fewer than 0.07% of childhood malignancies[1,2]. Presently, treatment of this disease continues to be frustrating and prognosis remains poor. The overall prognosis of MM in childhood appears to be as unfavorable as the adult counterpart, but some pediatric cases with MM with long-term survival have been reported[3,4]. We describe a case of pleural MM in a child with long-term survival who gave a complete response to ICE (ifosfamide, carboplatin, etoposide) - VAC (vincristine, adriamycin, cyclophosphamide) chemotherapy regimen.

Case Report

An eight-year-old girl presented in March 1997 with fever, cough, shortness of breath, and left-sided chest pain of 15 days' duration. She had been previously well except for weight loss of one kilogram during the last month. Her past and family history were both unremarkable.

On admission, physical examination revealed tachypnea, dyspnea, markedly decreased breath sounds and dullness to percussion at the left middle and basal lung regions. Complete blood count findings were consistent with slight anemia and leukocytosis. She had an erythrocyte sedimentation rate of 130 mm/h and serum fibrinogen level of 7 g/dl (normal range 2-4 g/dl). Renal and liver function tests were within normal limits, except for the albumin level which was low (2.5 g/dl). Chest X-ray showed a large left-sided pleural effusion. An attempt at thoracentesis failed to obtain fluid. Thoracal USG (ultrasonography) showed no free fluid but revealed multiloculated cystic lesions occupying the pleural space. Using USG-guided thoracentesis, some pleural fluid was aspirated which was straw-colored with a specific gravity of 1010 and a LDH of 7,200 mg/dl. Cytological examination of the pleural fluid yielded 1,200 leukocytes/mm^3 with 74% lymphocytes and 26% polymorphonuclear leukocytes, and

negative results for malignancy. Chest computed tomography (CT) revealed a large loculated pleural effusion, areas of pleural thickening and passive atelectasis (Fig. 1). Cultures gave negative results for non-specific agents and mycobacterium tuberculosis. No improvement was obtained with an empirical antibiotic combination. It was decided to proceed to exploratory thoracotomoy and open biopsy since the unilateral pleural effusion was unresponsive to antibacterial therapy and since the massive effusion could not be drained because of loculated and multicystic characteristics of pleural lesions. Intraoperative findings disclosed fibrous white plaques occupying the entire left lung surface. Left pleura showed extensive adherence but cleavage was made along the lung tissue and successful decortication was performed. Decortication material consisted of

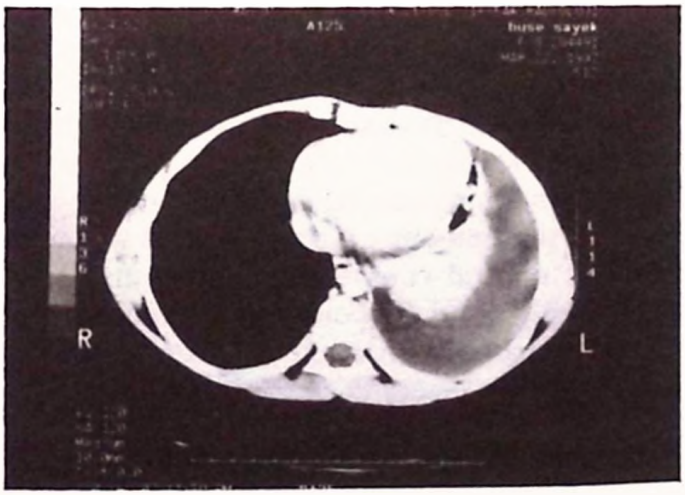

Fig. 1. Axial computed tomography scan shows a large left-sided pleural effusion and passive atelectasis.

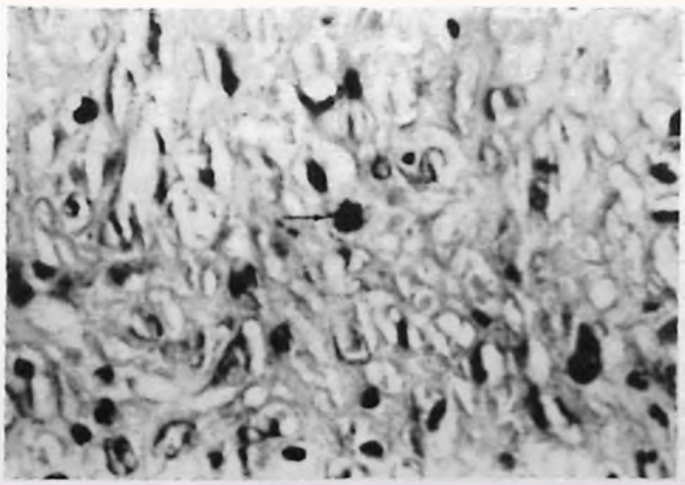

Fig. 2. Photomicrograph of the malignant mesothelioma with atypic, oval to elongated cells and an atypic mitotic figure (arrow) (H.E. stain, original magnification × 400).

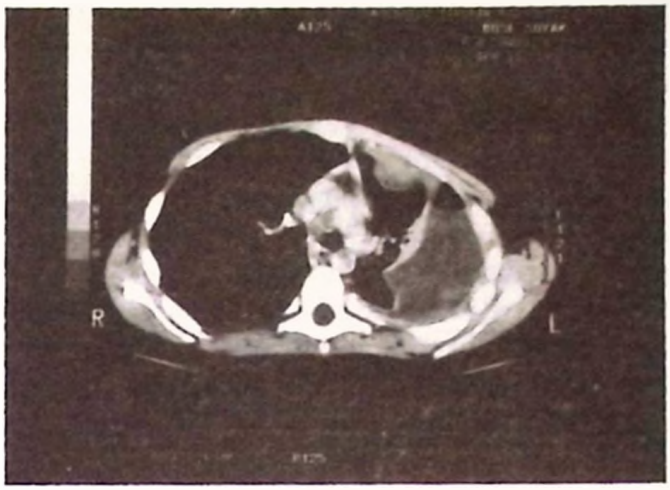

Fig. 3. Post-surgical computed tomography scan demonstrates a new pleural based solid mass of 2 cm in anterior chest wall accompanying the pleural effusion in the left hemithorax.

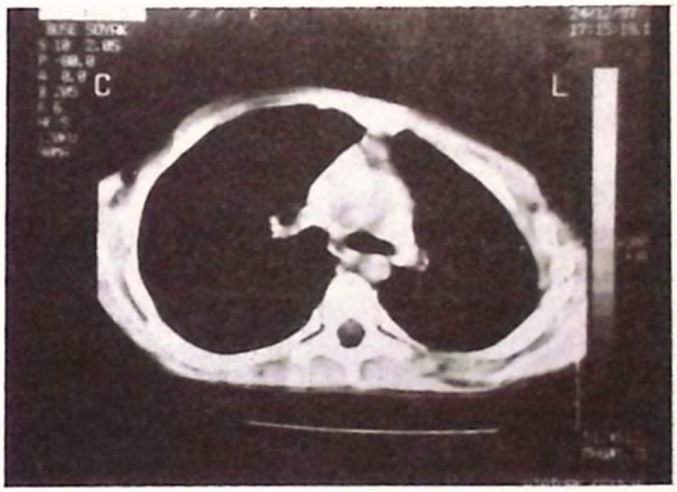

Fig. 4. Chest computed tomography showing only minimal pleural thickening on the left.

grayish-white, firm tissue covered with fibrin on one surface, measuring 14×5×0.8 cm. Microscopic examination showed the entire pleura to be thickened by neoplastic process. The tumor was highly cellular, made up of interwoven bundles of spindle cells which were immunohistochemically positive for both vimentin and keratin. Neoplastic cells showed nuclear atypia and occasional mitotic figures (Fig. 2). Histopathological diagnosis was sarcomatoid malignant mesothelioma. No history of environmental asbestos or another unusual exposure could be obtained either for the patient or for the family with subsequent questioning.

Postoperative CT showed a new 2 cm pleural based solid mass adjacent to the chest wall at the level of the carina. Again noted were large

loculated fluid collections in the left hemithorax (Fig. 3). After decortication, combination chemotherapy was started with ICE (ifosfamide 1.5 gr/m² + MESNA day 1-3; carboplatin 500 mg/m² day 3; etoposide 100 mg/m² day 1-3) alternating with VAC (vincristine 2 mg/m²; adriamycin 60 mg/m²; cyclophosphamide 600 mg/m² on day 1) with three-week intervals. The first course (ICE-VAC) resulted in significant clinical improvement in terms of dyspnea and tachypnea, and control CT showed a marked regression in the amount of effusion and disappearance of the extrapleural solid mass. A complete clinical and radiological response was obtained with six courses of chemotherapy; chest CT revealed only minimal diffuse pleural thickening at the level of left upper lobe (Fig. 4). The patient received no further therapy, and has been monitored with close clinical and radiological examination. Total follow-up period reached 36 months after discontinuation of therapy without any disease recurrence.

Discussion

Malignant mesothelioma rarely occurs in childhood; only an estimated 2-5% of all cases present in the first two decades of life[5]. The majority of mesotheliomas in children originate in the pleura as in the adult cases[2,4-6]; however, some less frequently encountered sites have also been reported, including the peritoneum[3,7], pericardium[8] and tunica vaginalis[9]. In contrast to the adult MM, there is little information concerning MM of childhood, and the etiology, epidemiology, natural course of the disease and optimal treatment strategies for this rare tumor of childhood are not well known. For the presented case, no history of exposure to asbestos or any other hazardous material in the patient's environment was obtained. Although there is a wealth of evidence supporting a strong association between asbestos exposure and MM in adults, no such clear causal association has been documented in MM of childhood[2,5,6]. A recent study on genetic epidemiology of malignant mesothelioma suggested an autosomal dominant pattern of inheritance for this tumor[10]. The family history of the presented case did not reveal any individual with mesothelioma.

Treatment of pleural MM in adults continues to be frustrating regardless of the modality employed. It is unresponsive to most chemotherapy and radiotherapy regimens, and it typically recurs even after the most aggressive attempts at surgical resection[11,12]. The outlook for pediatric patients with diffuse MM remains poor as in the adult patients. In localized tumors, resection is curative, but diffuse or invasive MMs, as seen in our patient, show poor prognosis since complete surgical resection is usually not possible. Brenner et al.[4] reported seven pediatric cases of MM and concluded that surgery and radiotherapy were not effective in controlling the disease in most of the cases.

Malignant mesothelioma was not a presumptive diagnosis for this patient while discussing thoracotomy since this tumor is extremely rare in this age group. The patient underwent exploratory thoracotomy and decortication with both diagnostic and therapeutic intent. After histopathologic diagnosis of MM, a second operation including pneumonectomy and also radiation therapy were discussed but, in an attempt to avoid the potential morbidity in a very young child, it was decided to employ these treatment modalities only in case of therapy failure. Systemic chemotherapy was the choice for this patient since some tumors show a different natural course in children and give surprisingly good response to chemotherapy when compared with adult counterparts.

Numerous trials of chemotherapeutic agents have been performed, but no chemotherapy regimen has yet emerged as an effective treatment for pleural MM[12]. However, among the chemotherapy agents that have been tested in adults, the anthracyclines, platinum compounds, and alkylating agents have demonstrated small but real activity against mesothelioma[11,13]. Although MM usually gives poor response to chemotherapy, some cases with response to adriamycin or to a combination containing adriamycin and cisplatin have been reported[11-13]. A few pediatric cases who gave a complete response to chemotherapy have been reported with vincristine, adriamycin, cyclophosphamide combination[4], and with ifosfamide[14]. Varan et al.[15] reported an adolescent boy with pleural MM who gave a very good response to a combination regimen containing vincristine, adriamycin, ifosfamide and cisplatin.

We combined ICE regimen with VAC regimen. The former combination has been shown to be

effective in resistant and relapsed solid tumors of childhood[16,17]. While the latter is a well documented combination for its efficacy in various malignant soft tissue tumors of childhood.

In conclusion, we obtained a complete response and a long-term survival with this combination. The efficacy of ICE-VAC regimen in MM merits further evaluation. Because of the very small number of pediatric patients with MM at each institution, multi-institutional trials are necessary to approach this rare tumor of childhood in an efficient manner.

REFERENCES

1. Coffin CM, Dehner LP. The soft tissues. In: Stocker JT, Dehner LP (eds). Pediatric Pathology (1st ed). Philadelphia: J.B. Lippincott Company; 1992: 1091-1132.
2. Fraire AE, Cooper S, Greenberg SD, et al. Mesothelioma of childhood. Cancer 1988; 62: 838-847.
3. Geary WA, Mills SE, Frierson HF, et al. Malignant peritoneal mesothelioma in childhood with long term survival. Am J Clin Pathol 1991; 95: 493-498.
4. Brenner J, Sardillo PP, Magill GB. Malignant mesothelioma in children: report of seven cases and review of the literature. Med Ped Oncol 1981; 9: 367-373.
5. Kelsey A. Mesothelioma in childhood. Pediatr Hematol Oncol 1994; 11: 461-462.
6. Grundy GW, Miller RW. Malignant mesothelioma in childhood. Cancer 1972; 30: 1216-1218.
7. Armstrong GR, Raafat F, Ingram L, Mann JR. Malignant peritoneal mesothelioma in childhood. Arch Pathol Lab Med 1988; 112: 1159-1162.
8. Eker R, Cantez T, Doğan Ö, et al. Pericardial mesothelioma: a pediatric case report. Turk J Pediatr 1989; 31: 305-309.
9. Plas E, Riedl CR, Pflüger H. Malignant mesothelioma of the tunica vaginalis testis. Cancer 1998; 83: 2437-2446.
10. Roushdy-Hammady I, Siegel J, Emri S, et al. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 2001; 357: 444-445.
11. Sterman DH, Kaiser LR, Albelda SM. Advances in the treatment of malignant pleural mesothelioma. Chest 1999; 116: 504-520.
12. Ryan CW, Herndon J, Vogelzang NJ. A review of chemotherapy trials for malignant mesothelioma. Chest 1998; 113: 668-738.
13. Krarup-Hansen A, Hansen HH. Chemotherapy in malignant mesothelioma: a review. Cancer Chemother Pharmacol 1991; 28: 319-330.
14. Pratt CB, Meyer WH, Douglass EC, et al. Phase I study of ifosfamide with mesna given daily for three consecutive days to children with malignant solid tumours. Cancer 1993; 71: 3661-3665.
15. Varan A, Kara A, Haliloğlu M, et al. Malignant mesothelioma in an adolescent boy. Pediatr Int 1999; 41: 693-695.
16. Kung F. Ifosfamide/Carboplatin/Etoposide (ICE) for recurrent childhood malignant solid tumours: a review. Int J Ped Hematol Oncol 1995; 2: 405-410.
17. Sarıalioğlu F, Olgun N, Uysal KM, et al. Carboplatin-based chemotherapy for refractory or relapsed childhood solid tumors. Med Ped Oncol 1996; 27: 345.