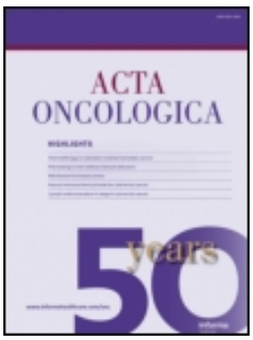

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

A multimodality approach to reversible paraneoplastic encephalitis associated with ovarian teratomas

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To cite this article: Tiffany Tang, Kay Yaw Tay, Tiffany Tang, Kay Yaw Tay, Josiah Chai, Anupriya Agarwal, Jeffrey Low, Ee Lian Lee, Khoon Leong Chuah, Kesavan S/o Sittampalan, Chin Fong Wong, Josep Dalmau, Joanne Ngeow, Lay Tin Soh & Min-Han Tan (2009) A multimodality approach to reversible paraneoplastic encephalitis associated with ovarian teratomas, Acta Oncologica, 48:7, 1079-1082, DOI: 10.1080/02841860902829221

To link to this article: https://doi.org/10.1080/02841860902829221

Published online: 08 Oct 2009.

Pathology diagnosis is achieved through biopsy. As in our case, biopsies do not always yield the expected results. We should not forget that this test may also sometimes give false positive results, especially in low-grade AS that cannot be readily distinguished from radiotherapy-induced changes [3].

Standard therapy entails surgery with complete tumour resection. However, as in our case, chemotherapy becomes the first treatment of choice when surgery is not possible.

Results are far from alone promising for the most widely used drugs. Anthracyclines alone or with iphosphamide have led to disease control after several months (between 7 and 24 months) [8], always in combination with previous surgery. Over the past few years, paclitaxel has been used for used in advanced stage and/or metastatic AS [9,10].

In our case, the weekly taxane kept the disease under control for five months. Our case reveals the sound profile of paclitaxel as a single agent in the initial treatment of unresectable, radiotherapy-induced AS in an anthracycline-naïve patient.

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A multimodality approach to reversible paraneoplastic encephalitis associated with ovarian teratomas

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Paraneoplastic encephalitis associated with ovarian teratomas and antibodies to the N-methyl-D-aspartate receptor (NMDA) is a recently described phenomenon and resection of the tumour appears significant in achieving sustained neurological recovery [1]. We describe two patients who presented

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(Received 16 November 2008; accepted 16 February 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860902829221

with paraneoplastic encephalitis associated with immature teratomas and discuss the role of chemotherapy in the treatment of this condition.

The first patient was a 15-year-old girl who presented with lower abdominal pain. A CT scan of her pelvis revealed bilateral ovarian masses suggestive of teratomas. These were resected and histology of the left ovarian tumour revealed a grade (2/3) immature ovarian teratoma and the right ovarian cyst had features suggestive of a benign cystic teratoma. With further omental foci of immature teratoma she had a final pathologic stage of IIIA. Twenty-five days post operatively, she began to exhibit several neuro-psychiatric symptoms which include marked short-term memory loss, paranoid psychosis, agitation, catatonia and myoclonic jerks. No organic cause was found to explain her symptoms; extensive metabolic and imaging studies were normal, serum anti-neuronal antibodies (anti-Hu, anti-Yo and anti-Ri) were negative and an EEG done was unremarkable. After failing treatment with anti-psychotic agents, she was started on standard BEP (bleomycin, etoposide, cisplatin) chemotherapy; 14 days after her symptoms began. Two weeks after initiation of chemotherapy her paranoid psychosis resolved. Six weeks later and after completion of three cycles of BEP, her memory returned to normal and she recovered completely.

The second patient was a 24-year-old woman who presented with vomiting and diarrhoea preceding fever, fits and altered mental status. On examination, she had gaze-evoked nystagmus and dystonia. She was also seen with intermittent eye deviation and version to the right associated with right upper limb rigidity and clenching of her fist. She would shout, speak incomprehensibly and she would not respond appropriately to external verbal or visual cues. CSF examination revealed leukocyte pleocytosis, with a nucleated cell count of 14/ul (95% lymphocytes, 5% monocytes, 0% neutrophils); CSF glucose was 3.9 mmol/L with a blood glucose level of 5.4 mmol/L; CSF protein was within normal range. Microbiological assessment of CSF for bacteria, mycobacterium, fungi and viruses were negative and MRI scans of the brain revealed several small T2 hyperintense foci in bilateral cerebellar hemispheres (Figure 1). The patient was treated empirically for bacterial and herpes simplex encephalitis and in view of her failure to respond to the initial antibiotic regimen, she was also treated for tuberculous meningoencephalitis. In search of a paraneoplastic cause to explain her symptoms, a CT scan of her thorax, abdomen and pelvis was performed. This revealed a 10.8 by 9.7 by 8.5 cm cystic lesion suggestive of a left-sided ovarian teratoma (Figure 2). Examination of the patient's serum for paraneoplastic markers (anti-Hu, anti-Yo and anti-Ri) was negative. Immunological characterisation of her serum and CSF demonstrated the presence of anti-NMDA receptor autoantibodies. She underwent a resection of the left-sided teratoma (Figure 3) and intra-operatively, a right ovarian cyst was seen and removed. Histology revealed a grade (3/3) immature teratoma and a mature teratoma respectively with a final

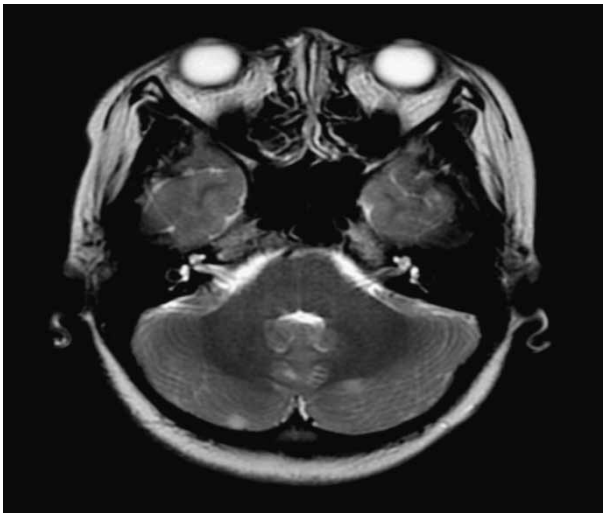

Figure 1. MRI showing T2 hyperintensities in bilateral cerebellar hemispheres in Patient 2

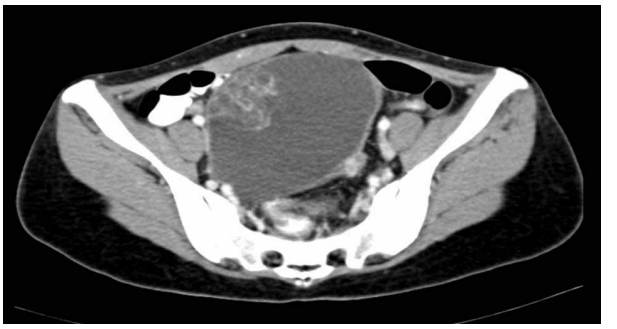

Figure 2. CT pelvis showing the left sided teratoma in Patient 2

Figure 3. Macroscopic appearance of the left ovarian teratoma from Patient 2

Table I. Paraneoplastic Encephalitis associated with Immature Ovarian Teratomas (IOT)–Outcomes with and without chemotherapy.

Reference	Age/ Gender	Tumour Diagnosis and stage as published	Anti-Neuronal antibodies	Treatment	Outcomes
Dalmau [1]	Case 1 (30/F)	10 cm right IOT	NMDA R (+)	Corticosteroids Plasma exchange IVIG Tumour Removal	Back to work as an internal medicine resident
	Case 4 (17/F)	7 cm left IOT	NMDA R (+)	Plasma Exchange IVIG Tumour Removal Corticosteroids and Cyclophosphamide	Back to school with good grades
	Case 7 (19/F)	22 cm right IOT	NMDA R (+)	Corticosteroids IVIG Tumour removal **Chemotherapy**	Alternating insomnia/hypersomnia for 7 months; total recovery of motor function but MMSE 24/30
	Case 10 (14/F)	1.9 cm left IOT	NMDA R (+)	Tumour removal Plasma Exchange Corticosteroids IVIG	Unexpected death after mild improvement
Aydiner [2]	39/F	6.8 cm benign ovarian teratoma with 1 mm focal area of immature component	Anti-Hu and Anti-Yo from serum and CSF negative	Tumour removal **Chemotherapy (BEP)**	Mood disorder controlled with Lithium Persistent amnesia
Sansing [3]	34/F	7.9 cm left IOT	NMDA R (+)	Tumour removal Methylprednisolone Plasma Exchange IVIG Cyclophosphamide **Chemotherapy**	Mild generalized weakness but could walk unaided. Normal cognitive function, memory and psychiatric evaluation.
van Altena [4]	32/F	5 cm IOT in both ovaries Grade 1, Stage Ib	Anti-Hu, Anti-Yo, Anti-Ri, Anti-Tr, Anti-amphi, Anti CV2, anti-Ma2 in CSF and serum negative	Bilateral salpingo-oopherectomy only	Normal Neurological and Performance status
Lee [5]	15/F	20 cm left IOT and 12 cm mature teratoma in the right ovary	Not reported	Tumour removal Methylprednisolone	Expressive aphasia Disorientation in time and date Continued to drop out of school
Nokura [6]	19/F	IOT	Negative for Anti-Hu	Tumour removal Corticosteroids	Memory problem and poor score on IQ testing at 6 months

pathologic stage of IA. Her neuropsychiatric symptoms failed to abate despite surgery and a course of intravenous immunoglobulins. Fourteen days postoperatively, she was started on adjuvant chemotherapy with a standard chemotherapeutic regime of BEP, receiving a total of three cycles. Her dystonia became less prominent rapidly after initiation of her first cycle, but it was only after 20 days after commencement of chemotherapy that she regained orientation and was able to answer questions in a relevant and appropriate manner. She returned to work four months after completion of chemotherapy.

These two cases highlight the role of chemotherapy as an adjunct to surgery in a multimodality approach to paraneoplastic encephalitis associated with teratoma. In the first patient, the temporal association is definitive where neuropsychiatric symptoms only developed after the teratomas were resected. These symptoms resolved completely following chemotherapy. Given that tumour foci were identified on the omentum and in the peritoneal fluid, it is conceivable there may have been residual disease after surgery resulting in a delayed onset of encephalitis. This would further support the role of chemotherapy as an adjunct to surgery. In the second patient, since both surgery and intravenous immunoglobulin was administered prior to chemotherapy, one cannot exclude the possibility that her improvement may have represented a delayed effect of treatment. However, a strong temporal association between initiation of chemotherapy and symptom improvement was noted.

In a review of patients reported to have paraneoplastic encephalitis associated with immature ovarian teratomas in the English literature (Table I), only three of the ten patients received chemotherapy, with a fourth receiving cyclophosphamide only [1–6]. The grade and stage of the disease as well as the details of treatment were however not reported for all ten patients so it is unclear whether chemotherapy would have been recommended [7,8]. The current difficulty in establishing ideal treatment modalities lies in the small number of patients that have been identified to date and further reports may be helpful to determine this.

Acknowledgements

Dr. Min-Han Tan has received support for research by the Singapore Millenium Foundation.

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Somatic mutation of GNAQ gene is rare in common solid cancers and leukemias

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(Received 16 November 2008; accepted 16 February 2009)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860902882444