

LETTERS TO THE EDITOR

Role of radiotherapy in adult ganglioneuroblastoma and ganglioneuroma

Dear Editor,

Ganglioneuroma (GN) and ganglioneuroblastoma (GNB) are a subset of peripheral neurogenic tumors. They are grouped according to their neuroblastic grade of differentiation, type, malignant potential and schwannian stroma development [1]. They are mostly seen in mediastinum, followed by retroperitoneum, adrenals, neck, and pelvis [2,3]. GN is a rare, benign and slow growing tumor. It is usually seen in children. While the prognosis of GN is favorable, GNB has a poor prognosis. Therefore, careful distinction must be made between the two [1-3].

The goal of primary treatment of GN and GNB is complete surgical excision [2,4,5]. It is curative and recurrences haven't been reported after removal [1]. But, in a small number of cases, lymph node metastasis adjacent to tumor, metastasis to distant organs and unresectable cases were reported. In such situations, in order to control tumor growth and induce regression, radiotherapy or, especially in children, chemotherapy is recommended. In GN treatment there is no room for preoperative/postoperative chemotherapy or radiotherapy, but in GNB treatment, although without full consensus, chemotherapy or radiotherapy is recommended after surgery [2,4,5].

In conclusion, because of their rarity, it is difficult to analyze treatment options for these tumors. They were first described in 1965. After this period, a large number of cases have been published regarding GN and GNB. Treatment plans were created based on follow-up of these patients. Surgical excision is the primary treatment but in inoperable, unresectable and metastatic cases, radiotherapy should be considered for symptom palliation associated

with metastatic masses.

References

1. Shetty PK, Balaia K, Gnana Prakash S et al. Ganglioneuroma always a histopathological diagnosis. Online Journal of Health and Allied Sciences 2011;9:1-3.
2. Okudera Y, Miyaskoshi N, Sugawara T et al. Ganglioneuroblastoma of filum terminale: Case report. J Neurosurgery 2014;21:270-274.
3. Sasaki A, Suto T, Nitta H et al. Laparoscopic excision of retroperitoneal tumors: report of three cases. Surg Today 2010;40:176-180.
4. Petricevic J, Librenjak D, Tomic S et al. Adrenal ganglioneuroma in an adult - case report. Psychiatr Danub 2014; 26 (Suppl 2):407-408.
5. Raina V, Kamble R, Tamwar R et al. Spinal ganglioneuroblastoma--complete response to chemotherapy alone. Postgrad Med J 1993;69:746-748.

Yasemin Benderli Cihan¹, Aynur Aytakin¹, Talha Sarigoz²

¹Kayseri Education and Research Hospital, Department of Radiation Oncology, Kayseri; ²Kayseri Education and Research Hospital, Department of General Surgery, Kayseri, Turkey

Correspondence to: Yasemin Benderli Cihan, MD.
E-mail: cihany@erciyes.edu.tr

Juvenile granulosa cell tumor of the testis in a newborn

Dear Editor,

Granulosa cell tumor of the testis is a benign very rare sex cord stromal tumor that can be distinguished in the adult and juvenile type. The juvenile type (JGCT) of the testis is a benign hormonally inactive neoplasm, mor-

phologically similar to its ovarian counterpart, with good prognosis. It usually occurs in the first months of life with 90% of the cases being reported in less than one year old males [1].

A 15-day old male was referred to the pediatric clinic with a right scrotal swelling. Apart from a painless mass in

the right testis, his physical examination was unremarkable with no dysmorphic features or ambiguous genitalia. He was born at term with a birth weight of 3.750 gr. Antenatal and perinatal history were uneventful.

Testicular sonography revealed a 1.62x1.15 cm well circumscribed mass, with multicystic spaces containing thick liquid (Figure 1) and presence of vascularization among the cystic spaces on color Doppler sonography. Abdominal ultrasound was normal. Karyotype was 46XY. Hormonal profile showed normal values for his age, normal β -HCG, AMH and inhibin B and raised α -fetoprotein (AFP) 2021U/ml, normal for his age.

Macroscopic evaluation of the testicular tissue after orchiectomy revealed a well circumscribed multilocular cystic mass containing serosal fluid. This was microscopically characterized by a lobular growth pattern, with variably sized and shaped follicles containing basophilic material and lined by cells with oval nuclei, abundant eosinophilic cytoplasm and rare mitotic activity. Immunohistochemically, the cells were positive for inhibin, vimentin, smooth muscle actin, protein S-100 and Ker AE1/AE3 and negative for AFP. The pathology report confirmed the diagnosis of JGCT of the testis.

Testicular and abdominal ultrasonography, and a chest radiograph two months after surgery were normal. He was scheduled for regular follow up visits at 6-month intervals for the first two years and yearly thereafter until at least 5 years. At 18 months our patient is healthy and serum AFP levels progressively declined to normal values for his age.

Only 63 cases were reported up to 2014 [2] in an extensive search of the literature. In a more recent review Kao et al. collected and described the clinicopathological features of 70 cases [1]. Orchiectomy by an inguinal or subinguinal approach is the therapy of choice. Many authors, however, propose that in the absence of raised AFP and/or β -HCG testicular sparing surgery can be considered in patients with small well circumscribed tumors [3,4].

Consensus guidelines for the follow up management of these patients are not available. Some authors support that follow up is not required after surgical removal of the testis [3], while others propose a follow-up for at least 5 years as for most other tumors [5].

In conclusion, although neonatal testicular tumors are rare, our case confirms the need of consideration of a testicular tumor in the differential diagnosis of scrotal masses in newborns. JGCT should be suspected in neonates presenting at birth and infants with a painless complex, cystic mass of the testis.

References

1. Kao CS, Cornejo KM, Ulbright TM, Young RH. Juvenile granulosa cell tumors of the testis: a clinicopathologic study of 70 cases with emphasis on its wide morphologic spectrum. *Am J SurgPathol* 2015;39:1159-1169.
2. Rane SU, Menon S, Desai S, Bakshi G, Joshi A. Granulosa cell tumor of testis: Clinicopathological correlation of a rare tumor. *Indian J Pathol Microbiol* 2014;57:564-573.
3. Shukla AR, Huff DS, Canning DA et al. Juvenile granulosa cell tumor of the testis: contemporary clinical management and pathological diagnosis. *J Urol* 2004;171:1900-1902.
4. Cosentino M, Algaba F, Saldaña L et al. Juvenile granulosa cell tumor of the testis: a bilateral and synchronous case. Should testis-sparing surgery be mandatory? *Urology* 2014;84:694-696.
5. Seixas-Mikelus SA, Khan A, Williot PE et al. Three-month-old boy with juvenile granulosa cell tumor of testis and ossifying renal tumor of infancy. *Urology* 2009;74:311-313.

Feneli Karachaliou¹, Angeliki Nika², George Simatos¹, Marina Vakaki³, Margarita Baka⁴

¹Department of Endocrinology, ²Neonatology, ³Radiology and ⁴Oncology, "P&A Kyriakou" Children's Hospital, Athens, Greece

Correspondence to: Dr. Feneli Karachaliou.

E-mail: fenkar1@hotmail.com

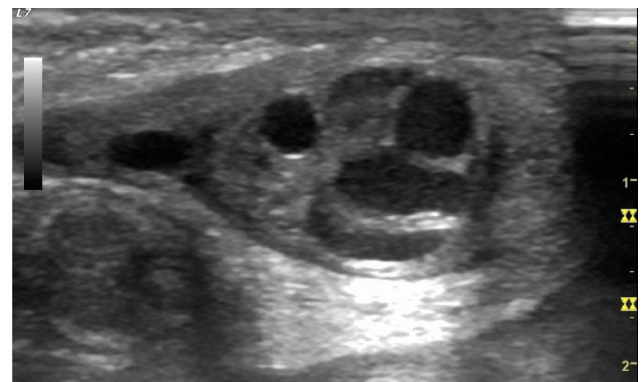


Figure 1. Ultrasonography of the right testis revealing a mass with multicystic spaces.

Abiraterone acetate as a possible cause of sudden cardiac death

Dear Editor,

The most common cause of death in patients with

metastatic castration-resistant prostate cancer (MCRPC) is disease progression. The incidence of sudden cardiac death (SCD) occurring in patients with MCRPC is un-

common and similar to this seen in normal population. Abiraterone acetate (AA) is a safe and relatively new drug which provides a favorable survival outcomes in patients with prostate cancer [1]. Early trials endorsed the activity of AA with regard to decrease of PSA levels in patients with MCRPC who had not been treated with a previous chemotherapy. Despite survival improvement with the use of AA, there are some speculations in the literature regarding cardiac disorders such as heart failure, fatal arrhythmia and SCD [2,3]. Herein we would like to report a case of SCD in a patient with MCRPC that might be associated with the use of AA on the second day of drug initiation.

A 75-year-old man with clear past medical history started AA 1000 mg/day (Tabl. of 250 mg x4) as first-line treatment for MCRPC. On the second day of drug initiation, the patient was admitted to the emergency department with loss of consciousness. Electrocardiogram showed a left bundle branch block along with second degree atrio-ventricular block and ventricular tachycardia. The patient died shortly after from cardiac failure following ventricular arrhythmia. There was no other detectable cause of death related to non-cardiac reason.

A randomized double-blind placebo-controlled study has recently reported low rates of adverse events leading to death (2 vs 1%) in patients with MCRPC treated with AA after progression on docetaxel compared with the placebo arm [3]. According to full prescribing information of AA, cardiac failure developed more frequently in patients treated with AA compared to placebo (2.1 vs 0.7%). The rate of grade 3-4 cardiac failure in patients using AA and in those taking placebo was 1.6 vs 0.2%, respectively. One case of death associated with arrhythmia and one case of SCD were reported in the AA arm, while no death was observed in the placebo arm. There were 7 (0.5%) deaths due to cardiac arrest in the AA arm and 3 (0.3%) in the placebo arms [4]. On the other hand, no deaths due to AA were reported in a phase III trial comparing 1088 patients using AA with placebo. The most common cardiac events were grade 1 and 2 tachycardia and grade 3 or lower atrial fibrillation. Deaths due to side effects developed in similar proportions of patients in both groups [105 deaths;13%] in the AA group vs 61 (16%) in the placebo group [5].

From the information given above it is possible that the use of AA may increase the incidence of arrhythmias which are possible predisposing factors for fatal cardiac

arrhythmias. Similarly to our case, unknown cause of SCD or fatal cardiac arrhythmias may occur during treatment with AA. Such events associated with AA may discourage the physicians' confidence on the drug safety. On the basis of these findings, possible adverse events of AA with respect to SCD, should be investigated and clarified with placebo-controlled clinical trials.

References

1. De Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995-2005.
2. Procopio G, Grassi P, Testa I et al. Safety of abiraterone acetate in castration-resistant prostate cancer patients with concomitant cardiovascular risk factors. *Am J Clin Oncol* 2015;38:479-482.
3. Mulders PF, Molina A, Marberger M et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. *Eur Urol* 2014;65:875-883.
4. US Food and Drug Administration. FDA labelling information-Zytiga. FDA website [online], http://www.access-data.fda.gov/drugsatfda_docs/label/2012/202379s0051bl.pdf
5. Fizazi K, Scher HI, Molina A et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13:983-992.

Suleyman Sahin¹, Fatih Karatas¹, Tulay Eren¹, Mustafa Altinbas¹, Kadri Altundag²

¹Diskapi Yildirim Beyazit Training and Research hosp., Dept of Medical Oncology, Ankara; ²Hacettepe University Faculty of Medicine, Dept of Medical Oncology, Ankara, Turkey

Correspondence to: Kadri Altundag, MD
E-mail: altundag66@yahoo.com

Chromosomes 7/17 multiplication vs true polysomy: a crucial issue in lung and breast EGFR/HER2 dependent carcinoma cases

Dear Editor,

Based on an increasing need for applying targeted therapies in subgroups of patients, oncologists demand

molecular data derived by in situ hybridization (ISH) analyses. Concerning HER2/neu (17q21) and EGFR (7p12) on-cogenes, protein expression should be combined to gene numerical status in breast and non-small cell lung car-

cinomas (NSCLC), respectively, especially in borderline positive cases for immunohistochemistry (IHC) [1,2]. Although IHC implementation identifies protein overexpression in those critical for therapeutic reasons molecules, it does not provide data about the molecular mechanism that induces the corresponding expression. Fluorescence ISH (FISH) and chromogenic ISH (CISH) demonstrate a high concordance in evaluating numerical imbalances including HER2/neu and EGFR genes.

According to ASCO/ACAP 2013 updated recommendations, FISH/CISH with dual mainly color probes (EGFR/CEP7, HER2/CEP17; CEP: chromosome centromere) are interpreted as a ratio between overall gene copies (including small to large gene clusters) to overall centromeric spots in 20-40 well visualized intact, non overlapping nuclei [3]. Based on the extracted ratio, the genetic event is categorized as normal for numerical imbalances, gene amplification, gene deletion, and/or chromosome diploidy/aneusomy (polysomy or monosomy). Borderline cases demonstrated a gene/CEP ratio <2, but with an average gene copy number ≥ 6 signals per cell are diagnosed as positive for gene amplification. This is a very important approach and a progress for handling those cases by applying monoclonal antibodies (mAbs) increasing the number of patients that may achieve response and survival benefits. Based on the previous ASCO/CAP 2007 gene signals interpretation criteria, these cases were not considered eligible for anti-HER2 mAbs therapeutic regimens. Identification of intra-carcinoma genomic heterogeneity due to rise of different cancerous clones is the explanation for this modification

Concerning CEP signals, there is skepticism for interpreting them as a pure chromosome polysomy. FISH and CISH detect these centromeric copies, but do not reveal the exact genetic mechanism that produces them. Based on specific molecular analyses including microarray comparative genomic hybridization some studies support the idea that chromosome 17 polysomic breast adenocarcinoma cases defined by multiplication of CEP17 in FISH assays were frequently related to 17q gain involving centromeres or amplification of the centromeric region rather than whole chromosome multiplication (true chromosome 17 polysomy) [4]. For this critical reason, multiple CEP signals should be interpreted as CEP17 multiplication instead of using the traditional term, chromosome 17 polysomy [5].

In conclusion, identification of specific gene deregulation mechanisms regarding growth factor receptors (ie EGFR, HER2) is a crucial point for designing and applying targeted therapeutic strategies. Multiple chromosome centromeric signals detected by FISH/CISH analysis do not always reflect a true polysomy affecting the extracted gene/CEP ratio reliability. Concerning the clinical significance of centromeric gain/amplification, these misleading gene/CEP results explain in part the limited response rates in subgroups of patients treated by mAbs.

References

1. Vera-Roman JM, Rubio-Martinez LA. Comparative assays for the HER-2/neu oncogene status in breast cancer. *Arch Pathol Lab Med* 2004;128:627-633.

2. Sholl LM, John Iafrate A, Chou YP et al. Validation of chromogenic in situ hybridization for detection of EGFR copy number amplification in non small cell lung carcinoma. *Mod Pathol* 2007;20:1028-1035.
3. Wolff AC, Hammond ME, Hicks DG et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. *J Clin Oncol* 2013;31:3997-4013.
4. Aeri Kim, Hyung Chan Shin, Young Kyung Bae et al. Multiplication of Chromosome 17 Centromere Is Associated with Prognosis in Patients with Invasive Breast Cancers Exhibiting Normal HER2 and TOP2A Status. *J Breast Cancer* 2012;15: 24-33.
5. Yeh IT, Martin MA, Robetorye RS et al. Clinical validation of an array CGH test for HER2 status in breast cancer reveals that polysomy 17 is a rare event. *Mod Pathol* 2009;22:1169-1175.

Evangelos Tsiambas^{1,6}, Vasileios Ragos², Dimitra Grapsa³, Nikolaos Kavantzias⁴, Andreas Karameris⁴, Athanasios Stamatiopoulos⁵, Georgios Georgakopoulos⁶, Panagiotis P. Fotiades⁷, Efstratios Patsouris⁴, Konstantinos Syrigos

¹Dept of Immunohistochemistry & Molecular Biology, 401 GAH, Athens, Greece; ²Dept of Maxillofacial Surgery, School of Medicine, University of Ioannina, Ioannina, Greece; ³3rd Department of Medicine, Athens Medical School, "Sotiria" General Hospital, Athens, Greece; ⁴ Dept of Pathology, Athens Medical School, Athens, Greece; ⁵Dept of Thoracic Surgery, KAT Hospital, Athens, Greece; ⁶Dept of Internal Medicine, General Hospital of Thiva, Thiva, Greece; ⁷Dept of Surgery, Leicester General Hospital, Leicester, UK

Correspondence to: Evangelos Tsiambas, MD

E-mail: tsiambasecyto@yahoo.gr

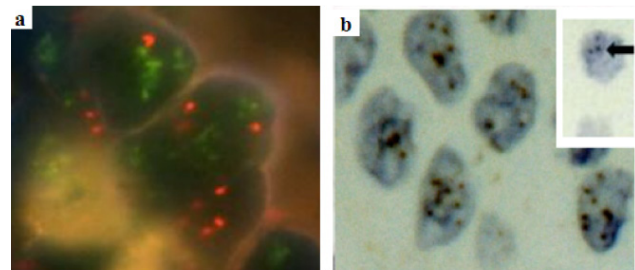


Figure 1. Multiple CEP copies: true polysomy or centromeric gains? **a:** HER2/CEP 17 amplified breast adenocarcinoma case. Red signals represent CEP17 copies, mainly 3 per nucleus (dual FISH analysis: HER2 green/CEP 17 red, original magnifications 400x); **b:** an EGFR/CEP 7 amplified NSCLC case. Brown signals represent EGFR multiple copies arranged isolated or in small clusters. Inside image shows CEP 7 multiple dark brown spots, 3 per nucleus (black arrow) (CISH analysis: EGFR and CEP 7 independent tissue sections, DAB staining, original magnifications 400x).

Erlotinib as first line treatment in a NSCLC patient with choroidal metastasis and with EGFR exon 19 deletion

Dear Editor,

A 62-year-old woman with no known history of disease experienced sudden loss of vision in the left eye. She was a smoker for up to 35 years. Ocular evaluation by fundoscopy and optical coherence tomography (OCT) revealed a solitary metastatic choroid tumor in her left eye. CT scans of the thorax and abdomen showed a spiculated mass 3x2.5 cm in the left upper lobe that surrounded the pulmonary artery and a hypodense mass 15x10 mm in the fourth segment of the liver. Positron emission tomography showed multiple distant metastases in the liver, left adrenal and bone. A transbronchial biopsy (TBB) was performed to diagnose adenocarcinoma of the lung. A final diagnosis of stage IV NSCLC was made and the patient received treatment with erlotinib. Genetic testing of the biopsied lung tumor detected an exon 19 deletion mutation of epidermal growth factor receptor (EGFR) in the primary tumor site. She had a dramatic improvement in the visual acuity by approximately 1 week after the start of treatment and 3 weeks later ocular examination showed complete regression of ocular metastasis. After 1 year of first-line therapy she still remains stable.

In November 2004, Food and Drug Administration (FDA) approved oral erlotinib as first-line treatment for patients with an EGFR mutation and second-line treatment in advanced NSCLC in case of relapse or disease progression after the first-line platinum-based combination treatment [2]. According to clinical studies, comparing erlotinib with standard chemotherapy, erlotinib conferred a significant progression-free survival benefit in patients with advanced EGFR mutation-positive NSCLC and was associated with more favorable tolerability. These findings suggest that erlotinib is important for first-line treatment of patients with advanced EGFR mutation-positive NSCLC [3]. Also, there are some few reports in the literature regarding EGFR treatment in choroidal metastasis. Thus, we also performed a PUBMED search of all relevant articles published in English until November 2015, using the key words "erlotinib" or "Tarceva" with "choroid", "choroidal", "uvea" or "uveal". The citations were reviewed in detail and the full text of each citation was obtained if available. All cases of lung cancer with choroidal metastasis treated with erlotinib were then included for further review.

There were only 7 cases regarding lung cancer with choroidal metastasis treated with erlotinib (excluding our

index case) (Table 1). Of these, 4 cases were in men, 5 cases lacked any information over the initiation time of erlotinib; 2 cases were treated with erlotinib as first-line treatment and 1 case has shown to have EGFR exon 19 deletion.

If further studies can support the initial findings, NSCLC patients with choroidal metastasis and with EGFR mutation could be treated with erlotinib as first-line treatment.

References

1. Herbst RS, Johnson DH, Mininberg E et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005;23:2544-2555.
2. Ye X, Kaliki S, Shields CL. Rapid regression of choroidal metastasis from lung cancer using erlotinib (Tarceva). *Oman J Ophthalmol* 2014;7:75-77.
3. Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-742.

Hakan Kocoglu¹, Mustafa Karaca², Rustu Turkyay³ Deniz Tural⁴

¹Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul; ²Gazi University Medical School, Internal Medicine, Medical Oncology Department, Ankara; ³Department of Radiology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul; ⁴Department of Medical Oncology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Correspondence to: Deniz Tural, MD.

E-mail: deniztural@gmail.com

Table 1. Characteristics and important aspects of lung cancer patients with choroidal metastasis who were treated with erlotinib (previous reports and index case)

	PMID or PMCID number - First author	Gender	Age (years)	Histology	Metastatic sites (at the time of erlotinib treatment)	Erlotinib as first line treatment?	Proven mutation	Status of choro- idal metastasis after erlotinib
1	22732948 - Navneet Singh	M	53	adenocarcinoma	liver, left ad- renal, bone	no	no	?
2	PMC4134551 - Xuemei Ye	F	48	adenocarcinoma	brain, bone	yes	no	complete regres- sion
3	19628953 - Seong-Woo Kim	F	57	adenocarcinoma	?	no	no	complete regres- sion
4	22333641 - Koichi Fujiu	F	49	adenocarcinoma	?	yes	EGFR exon 19	? (improvement of visual acuity)
5	22483721 - Chun-Liang Lai	M	73	adenocarcinoma	?	no	no	not responded - disease pro- gressed
6	18454905 - Jawad Akhter Gillani	M	45	non-small cell carcinoma without further sub-typing	?	no	no	good response
7	25390927 - Anthony B. Daniels	M	43	adenocarcinoma	?	no	no	complete regres- sion
8	index case	F	62	adenocarcinoma	liver, left ad- renal, bone	yes	EGFR exon 19	complete regres- sion

PMID: PubMed identifier, PMCID: PubMed Central Identifier, M: male, F: female, EGFR: epidermal growth factor receptor