Conservative multimodal management of a primitive neuroectodermal tumor of the thyroid

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Abstract

Primitive neuroectodermal tumors (PNET) represent 1% of sarcomas. Head and neck peripheral PNETs have an intermediate prognosis between abdominopelvic disease and extremities. We here report the case of a 40-year old male who presented with primitive neuroectodermal tumor of the thyroid and was treated by multimodal treatment, including surgery, chemotherapy and intermediate dose radiotherapy. The patient is alive and fit with a functional larynx at 27 months. Multimodal treatments yield five-year survival rates of about 60%. Major drug regimens use vincristine, doxorubicin, ifosfamide or cyclophosphamide, dactinomycin and/or etoposide. Complete surgical excision is undertaken whenever possible to improve long-term survival. However, the relative radiosensitivity of tumors of the Ewing family, suggest multimodal treatment including adjuvant conformal radiotherapy in case of positive margins or poor response to chemotherapy rather than resection with 2-3 cm margins, which would imply laryngeal sacrifice for thyroid tumors. The role of expert rare tumor networks is crucial for optimal decision-making and management of such rare tumors on a case by case basis.

Introduction

Primitive neuroectodermal tumors (PNETs) belong to the Ewing family of tumors and represent 1% of sarcomas.[1-3] Largest head and neck series included at most 11 cases occurring in various sites.[4-6] Three-year survival rates are about 60% (52-88%). Head and neck peripheral PNETs have an intermediate prognosis between abdominopelvic disease (who fare much worse) and extremities.[6-7] The sole two published thyroid PNET cases had adverse outcomes,[8] but would probably merit pathology review given their association with malignant teratoma and the absence of cytogenetic examination in one. Ewing thyroid cases mostly occur in patients ≤30 years.[2,3,9]

Case Report

A 40 year-old male, with unremarkable past medical history self-referred to a tertiary-care hospital for rapidly-progressive neck swelling, in November 2010. Doppler ultrasonography (US) of the neck disclosed a 55 mm heterogenous oval hypervascular solid nodule in the upper left thyroid lobe and two centimetric hypovascular nodules in the lower lobe. Thyroid isthmus and right lobe were normal in echostructure and size. The larynx was not involved. There was no suspicious lymph node, namely in the levels III, IV and VI. Left isthmolobectomy, performed in January 2011, revealed a suspicious malignant tumor, with accidental per operative extra-capsular rupture. Small basophile round cells, mainly monomorphic, containing a small hyperchromatic nucleus often inconspicuous and a scant cytoplasm, suggested PNET on per-operative histological examination. The diagnosis of PNET was further confirmed upon pathological review with highly positive MIC2 antigen (CD 99) staining (Figure 1A,B) and FISH analysis showing a specific t(11;22)(q24;q12) translocation (Figure 1C). Salvage surgery of a relapsed para-isthmic nodule, performed two months following initial surgery, showed residual isthmic tumor in the anterior neck tissues and along the right the cartilage ail. Conservative surgery was performed with thorough resection of all soft tissues along the external parts of the thyroid cartilage and hyoid bone. Given the non radical nature of the resection, the tumor was macroscopically removed but the margins were deemed microscopically positive. Following two cycles of chemotherapy (cisplatine, etoposide), chemotherapy was switched to doxorubicine and ifosfamide following subcutaneous tumor regrowth in the para-isthmic area, and yielded a complete response. Intensity modulated radiation therapy (IMRT) delivered 44 Gy to the thyroid bed with 3 cm cranio-caudal margins and 2 cm lateral and anteroposterior margins, 54 Gy to positive margins areas, and 60 Gy (Figure 1D) according to Euroewing 99 protocol based on response to chemotherapy and margins. The patient is alive without disease 27 months following the end of the multimodal treatment.

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Discussion and Conclusions

We here present the sole cytogenetically-confirmed published case of thyroid PNET with a presentation of rapidly-growing goiter. The diagnosis of PNET was suspected on extemporaneous examination showing small round cells. Central pathology review confirmed the suspicion of PNET. Ewing and PNET sarcomas share a similar histological appearance of small round blue cell tumor (except for the presence of rosettes), immunohistochemical markers, cytogenetic translocation t(11;22)(q24;q12) and MIC2 gene expression (both present in more than 90% of cases). An absence of neural differentiation supports a diagnosis of Ewing's sarcoma rather than that of PNET. Other differential diagnoses for other small, poorly differentiated, round cell tumors of the head and neck should malignant lymphoma, poorly differentiated salivary gland tumors, rhabdomyosarcoma, neuroblastoma, and undifferentiated nasopharyngeal carcinoma. Two cases were reported on the association between malignant teratoma and PNET but in the absence of cytogenetics, it is possible that the PNET component was indeed a more differentiated component of teratoma. If such association is reported in the future,

cytogenetics will be mandatory. Because of the rarity of those tumors, central pathological review was performed by an expert of the Groupe Sarcome Francais (GSF-GETO).

Based on a review of the literature of Ewing sarcomas/PNET (bone/soft tissues, ± head and neck cases), the optimal multimodality therapy of PNETs consists of neoadjuvant chemotherapy, surgery and radiation therapy based both on response to neoadjuvant chemotherapy and tumor site. Complete surgical excision with wide 2-3 cm margins is undertaken whenever possible to improve long-term survival.[10] In the current case, the initial clinical presentation led to rapid resection. However, the atypical goiter on US examination might have suggested malignancy, indicating to perform more radical surgery instead of limited resection. However, for such radiosensitive sarcomas as tumors of the Ewing family, wide resection with 2-3 cm margins, which would imply laryngeal sacrifice for thyroid tumors, for proximity reasons even if the larynx is not involved as was the case here, can be avoided using multimodality treatment. Indeed, radiotherapy is indicated in Ewing sarcomas whenever there are close or positive margins or poor response to chemotherapy (necrosis <90%). Adjuvant radiotherapy is associated with improved local control and improves survival when compared to surgery or radiotherapy alone. Intermediate radiation doses, no higher than 55-60 Gy. Normo-fractionated regimens with 1.8 or 2 Gy daily fractions, or bi-fractionated regimens with 1.5 Gy twice daily seem to be equally efficient. Exclusive radiation therapy is prescribed up to doses of 45-50 Gy on 3-cm-margin target volumes and up to 55-60 Gy on boost volumes. Additionally, owing to the relative chemosensitivity of tumors of the Ewing sarcoma family, chemotherapy (neoadjuvant or sequential) has a predominant part in the multimodal treatment. The Euro-EWING 99, a protocol involving several European oncology and pediatrics groups, propose chemotherapy protocols adapted to risk groups based on prognostic factors (metastasis, metastatic site if any, type of local treatment, histological response to neoadjuvant chemotherapy in operated patients, initial tumor volume <200 mL or >200 mL for non operable patients or undergoing preoperative radiationon) established according to the previous studies ET1, ET2, EW88, EW93, CESS81, CESS86, EICESS92. The protocol also includes radiotherapy based on the quality of resection and percent of tumor necrosis (10%).

Neoadjuvant chemotherapy aims at targeting occult micro-metastases and allowing tumor cytoreduction at the primary site. The type of adjuvant chemotherapy is chosen on the basis of the histological response, namely the percent of necrotic cells, to neoadjuvant chemotherapy. Major drugs regimens use vincristine, doxorubicin, ifosfamide or cyclophosphamide, dactinomycin (actinomycin D) and/or etoposide often in alternate VAC/IE-derived regimens. The rare case reports of PNET or Ewing head and neck/thyroid location have mostly used ifosfamide and etoposide. Multimodal treatments yield five-year survival rates of about 60% (52-88%) as reviewed in series including at least one case of Ewing sar-

Table 1. Previous cases.

Author	Patients	Median age (range)	Tumor characteristics (ES/PNET, bone/ soft tissues, M0/M1)	Tumor characteristics (head and neck sites)	Treatment characteristics for local disease	Outcomes
Allam[11]	24	17 (2-33)	24 ES bone 21 local/3 met	24 head and neck	Surgery, adjuvant chemo and sequential RT	5y OS 53%
Jurgens[12]	42	(1-23)	42 EFS 32 M0/10 M1	42 soft tissues 31 with bony involvement 4 head and neck	Surgery, adjuvant or noeadjuvant chemo and sequential postoperative RT	3y OS M0:56% M1:20%
Peng[13]	92	16 (1-72)	23 ES bone/21 soft tissues 43 PNET/5 Askin 57 M0, 35 M1	11 head and neck	Surgery, adjuvant or noeadjuvant chemo and sequential postoperative or exclusive RT	3y OS for M0 disease trimodal + surgery *vs* none = 74% vs 15%
Elomaa[14]	88	20 (5-65)	88 ES 84 of bone, 4 of soft tissues 73 M0, 15 M1	2 head and neck (mandible)	Neoadjuvant chemo, exclusive RT or surgery	M0 5y OS 70%, 5y DFS 58% M1 5y OS 28%, 5y DFS 27% 5y OS following R0 surgery 90%
Fizazi[16]	182	22 (15-55)	177 ES, 5 PNET	5 head and neck	Neoadjuvant chemo, surgery and postoperative RT (or exclusive RT)	5y OS 41%, DFS 32% 5y OS M0:54%, DFS 43%, median OS 61 m 5y OS M1:9%, DFS 6%, median OS 14 m
Verril[17]	59	24 (14-51)	ES of bone 25, of soft tissues 9 PNET soft tissues 19, PNET bone 5 unknown: 1	3 head and neck	Surgery, chemotherapy, adjuvant or exclusive RT	5y OS 38%, DFS 27%, median OS 41 m 5y OS M0: 52%, DFS 34%, median OS 61 m 5y OS M1: 8%, DFS 7%, median OS 15 m
Raney[18]	130	12 (1-20)	130 ES of soft tissues	8 head and neck	Upfront surgery, adjuvant chemo and sequential RT	10y OS 66%, DFS 60%
McLean[19]	82	13 (2-23)	PNET of bone: 7/82 ES of bone: 75/82	2 head/skull or head and neck	Upfront surgery, adjuvant chemo (or neoadjuvant) and sequential RT or exclusive RT	10y OS 48%, DFS 38% 10y OS 17%, DFS 12%
Paulino[20]	40	14 (2-58)	40 ES of bone	2 head and neck	Exclusive RT and sequential chemo	5y OS 55.5% 5 local relapse free survival 78.2%
Paulino[21]	76	15 (2-84)	76 ES of bone	6 head and neck	Upfront surgery, adjuvant chemo (or neoadjuvant) and sequential RT or exclusive RT	5y OS 57.5%
Grier[22]	518	57 (10-17)	ES of bone, PNET of bone 398 M0, 120 M1	23/398 head/skull or head and neck	Neoadjuvant chemo, surgery and postoperative RT (or exclusive RT)	M0: 5y OS 61-72% and 5y DFS 54-69% depending on chemo M1: 5y OS 34%, 5y DFS 22%

ES, Ewing sarcomas; PNET, primitive neuroectodermal tumors; RT, radiotherapy.

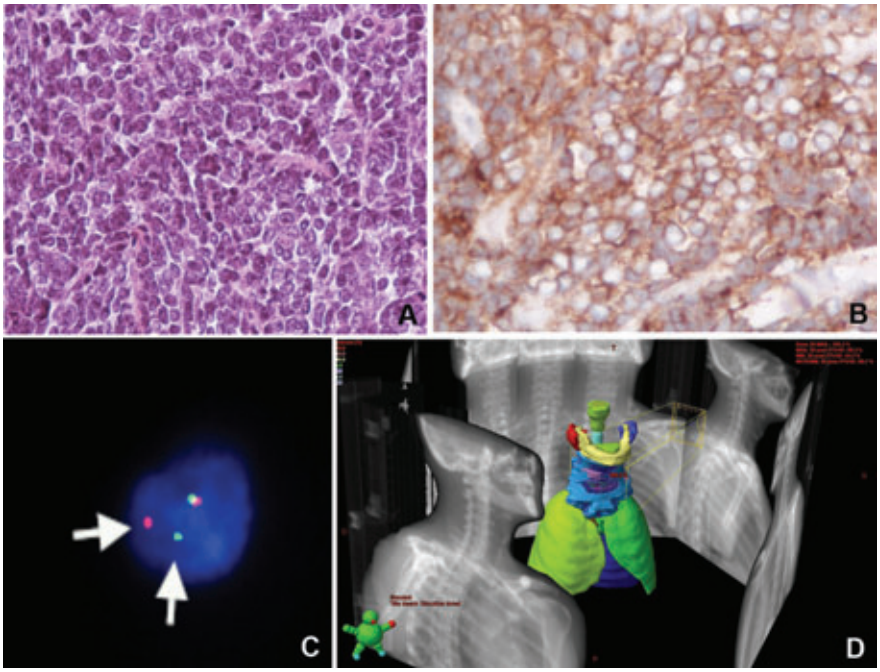

Figure 1. A) Uniform small round cells with round to oval nuclei and scanty eosinophilic or clear cytoplasm (HES, HFP x400). B) Immunohistochemical expression of CD99 showing characteristic reactivity on the cell membranes (HFP x400). C) Interphase fluorescence in situ hybridization (FISH) analysis using a two-color break-apart probe framing the EWSR1 gene at 22q12 (Vysis EWSR1 beak apart FISH probe, Abbott Molecular, Rungis, France). The rearrangement of the EWSR1 gene is detected by the split of the 5' (red signal) and 3' (green signal) (arrows) while the red and green fluorescent signals are juxtaposed on the normal allele. D) IMRT planification using 7 fields to treat three risk level volumes (44, 56, 60 Gy): 3D reconstruction and projected digital reconstructed radiographs.

coma/PNET of the head and neck (Table 1).[11-22] In the present case, local relapse happened very shortly after functional salvage surgery with large margins. The rapidity with which the relapse occurred may be explained by the tumor rupture at first surgery and by the relatively high growth kinetics of PNET and Ewing sarcomas. Therefore, chemotherapy followed by radiotherapy was indicated. Noteworthy, the patient's tumor responded poorly to cisplatin-etoposide chemotherapy but was responsive to second line doxorubicine-ifosfamide chemotherapy. The patient is alive and fit without disease and with a functional larynx 27 months after diagnosis.

Finally, this case report is the sole ever published cytogenetically-confirmed thyroid PNET. This case illustrates the difficulties to make the proper diagnosis upfront for such rare diseases presenting with unusual diseases sites. Complete surgical excision should be undertaken whenever possible to improve long-term survival. However, the relative radiosensitivity of the tumors of the Ewing family, suggest a multimodal treatment including adjuvant radiotherapy rather than wide resection, which would imply laryngeal sacrifice for thyroid tumors. New radiation therapy modalities may also contribute to good local control with laryngeal preservation.

This rare case report had a multimodal treatment and until last follow up has favorable outcome which suggests that the therapeutic strategy was adequate. However, this case is not generalizable and such rare cancer issues should rather be addressed on a case-by-case basis by local experts. Of note, rare tumor networks with designated experts like the GSF-GETO and the REFCOR (Reseau d'Expertise Francais des Cancers ORL Rares) are being created worldwide to build a straightforward streamline for physicians and patients dealing with rare tumors to guaranty optimal diagnosis and treatment.

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