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Twisted Plot of a Fairy Tale of Paediatric Germ Cell Tumour

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Abstract

Sacrococcygeal Teratoma (SCT) is a rare extragonadal Germ Cell Tumour (GCT). Incidence rates are reported from 1 in 14,000 to 1 in 29,000 live births [1]. Approximately 50 % of patients are diagnosed prenatally with a solid or multicystic mass in the coccygeal region and another 30 % with a sacral mass shortly after birth [2]. Extragonadal germ cell tumours are hypothesised to arise from germ cell precursors which are halted along their path of embryonic migration from yolk sac to gonadal ridge [3]. Surgical resection is the preferred treatment of SCT for mature and immature teratoma [1]. Recurrence of disease as growing teratoma syndrome or somatic-type malignancy is a rare but well-known and challenging clinical phenomenon. Transition or recurrence in terms of somatic malignancy is well documented phenomenon in adults with gonadal germ cell tumours, but very rarely documented in peadiatric age group [4]. Hence, we present this unique case series with two children with somatic transition. One child had somatic transition within teratoma at diagnosis and another had at relapse.

Abbreviations: SCT: Sacrococcygeal Teratoma; GCT: Germ Cell Tumour; MRI: Magnetic Resonance Imaging; AFP: Alpha Feto Protein; Beta HCG: Beta Human Chorionic Gonadotropin; PET scan: Positron Emission Tomography scan; FDG: Fluro-Deoxy Glucose; SMT: Somatic Malignant Transformation; PNET: Primitive Neuroectodermal Tumors.

Introduction

Sacrococcygeal Teratoma (SCT) is a rare extragonadal Germ Cell Tumour (GCT). Incidence rates are reported from 1 in 14,000 to 1 in 29,000 live births with a male: female ratio ranging of 1:2–1: 4. It mostly occurs during infancy and early childhood and belongs to the type I germ cell tumours [1]. SCT can be diagnosed prenatally with fetal ultrasound. Approximately 50 % of patients are diagnosed prenatally with a solid or multicystic mass in the coccygeal region and another 30 % with a sacral mass shortly after birth [2]. Extragonadal germ cell tumours are hypothesised to arise from germ cell precursors which are halted along their path of embryonic migration from yolk sac to gonadal ridge. They form tumours along the midline of the body, commonly head and neck, mediastinum, retroperitoneum and sacrococcygeal region [3]. Surgical resection is the preferred treatment of SCT for mature and immature teratoma [1]. In most cases, sacrococcygeal teratoma consists of benign tissue only. Presence of yolk sac components confirms malignant potential with a high recurrence risk. Recurrence of disease as growing teratoma syndrome or somatic-type malignancy is a rare but well-known and challenging clinical phenomenon. Transition or recurrence in terms of somatic malignancy is well documented phenomenon in adults with gonadal germ cell tumours [4]. But the transition and management are documented very rarely in paediatric extragonadal GCT. Hence, we present this unique case series with two children with somatic transition. One child had somatic transition within teratoma at diagnosis and another had at relapse.

Case Report 1

A six-year boy child presented with complaints of lower backpain and constipation for one year and urinary retention also for one week. On examination he had tenderness over tip of coccyx. Based on history and negative examination findings a clinical diagnosis of pelvic mass was kept. Magnetic Resonance Imaging (MRI) of abdomen and sacrococcygeal spine showed a large midline extraperitoneal pelvic mass, centred at lower end of sacrum and coccyx with solid-cystic components, heterogenous signal of size 7x7x10.8 centimetre (AP X Tr X CC). It was extending bilaterally from S1 to level below coccyx without intramedullary extension. There was no evidence of exopelvic component or infiltration. This was suggestive of sacrococcygeal teratoma. Tumor markers- Alpha Feto Protein (AFP) and Beta Human Chorionic Gonadotropin (Beta HCG) were normal. Hence, he underwent laparotomy and excision of tumour with coccygectomy. A transverse colostomy was done in view of direct infiltration of rectum. Post operative histopathology showed small round cells with hyperchromatic nuclei and scant cytoplasm

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with occasional rosettes. Immunohistochemistry was positive for CD 99 (cytoplasmic and focal membranous) and SALL-4. Negative for synaptophysin, chromogranin, LCA, Pan CK, SATB2. Impression was germ cell tumor with somatic differentiation of neuroectodermal type. FISH was negative for EWSR1 gene rearrangement. Positron Emission Tomography (PET) with Fluro-deoxy glucose (FDG) scan showed no residual and metastatic lesion. Hence, he was started treatment in the lines of Ewing sarcoma family of tumor protocol-AEWS 0031. Colostomy was closed four months later. Child has faecal continence. Child had completed proposed treatment. Reassessment PET scan showed complete response. Currently child is on follow-up six months post treatment and in remission.

Case Report 2

A six-year boy child presented with complaints of mass protruding from anal verge since birth and mass in left inguinal region for three months which gradually increased in size. There was no history of bladder or bowel disturbances. MRI showed lobulated ell defined soft tissue measuring 4.1x3x2.2 centimetre (AP X Tr X CC) in distal tip of sacral region. It was abutting lower sacral vertebra with no obvious erosion. There was no intraspinal extension. Few enlarged left inguinal lymph nodes largest measuring 2x1.1 centimetre. AFP was elevated with value of 600 IU/L. He underwent wide excision with left inguinal lymph node biopsy and then referred to our institution for further management with a diagnosis of sacrococcygeal yolk sac tumor.

On examination he had surgical scar in lower abdomen. Post operative AFP was normal. Post operative histopathology specimen showed morphology of poorly differentiated malignant neoplasm of glandular, squamous and immature epithelium. Immunohistochemistry (IHC) was positive for SALL4, glypican, focal CD 117, CK, S 100, INSM1 and diffuse CD 56. Negative for CD 30, OCT 4, SOX 11. It was suggestive of mixed germ cell tumor composed of immature teratoma (30%), yolk sac tumor (40%) with a component of neuroendocrine differentiation. Bone scan showed no evidence of skeletal metastasis. Bone marrow was not involved. Computerised Tomography (CT) scan chest was normal. Hence, he was diagnosed to have extragonadal germ cell tumor stage III. Categorised as high risk and was given four cycles of PEB (Cisplatin, Etoposide and Bleomycin). Post chemotherapy he underwent coccygectomy in order to prevent recurrence. Tumor markers were within normal limits. Post completion of treatment, PET scan done showed no evidence of FDG avid lesion at surgical site and elsewhere. Hence, he was kept under close follow-up.

Three months later child presented with recurrence of swelling in left inguinal region. Clinically he had firm left inguinal lymphadenopathy of 2x1 cm. Serum markers were normal (AFP -0.61 IU/ml, beta HCG -1.2 mIU/ml. Ultrasound abdomen was normal. Inguinal lymph node biopsy showed lymph node infiltrated with sheets, groups and cords of round to oval tumor cells with vesicular nuclei and prominent nucleolei. IHC was positive for SALL4, S 100, CD 56, CD 99 (focal), INSM1. Negative for CK, CD 30, OCT 4, NKX 2.2, SOX 11, GFAP, Desmin, WT 1, CD 117. HK27Me3 retained. Thus, immunomorphology suggestive of recurrent metastatic mixed germ cell tumor with somatic differentiation, probably neuroectodermal type. FISH was negative for EWSR1 rearrangement. Metastatic work up was negative. He was discussed in multidisciplinary tumor board and was started on treatment like Ewings tumor, He had completed proposed treatment. Reassessment PET analysis is normal. Hence, child is under follow-up.

Discussion

GCTs are rare in the paediatric age group and account for approximately 3% of cancers in children less than 15 years of age. They arise from the primordial germ cells which migrate from the yolk sac to the primitive gonadal ridge during embryogenesis. Arrest in migration of these cells may result in extragonadal GCTs. These are usually limited to midline locations like head and neck, anterior mediastinum, abdomen and the sacrococcygeal region. Sacrococcygeal region being the most common site for extragonadal GCTs in children. Sacrococcygeal teratoma may be diagnosed antenatally in foetal scan or later as a neonate, during infancy or early childhood. It could be benign or malignant. Teratomas with malignant transformation comprise up to 6% of metastatic teratomas [4]. While benign lesions may be managed with simple excision of the mass with coccygectomy, the malignant ones need multimodality approach including surgery and cisplatin-based chemotherapy [5].

Recurrences not only occur in case of malignant types of GCTs but may also develop after the resection of mature or immature teratomas [2]. Recurrence in benign counterpart is referred as growing teratoma syndrome [3]. Recurrence in malignancy can be with germ cell component or somatic-type malignancy. The latter is a rare but well-known and challenging clinical phenomenon. Transition or recurrence in terms of somatic malignancy is well documented phenomenon in adults with gonadal germ cell tumours [5]. During follow-up recurrence of lesion with normal tumour markers- serum Alpha Fetoprotein (AFP) or beta human chorionic gonadotropin (Beta HCG) can rise the suspicion of somatic transformation.

Like other GCTs, SCTs are composed of all three germ cell layers and may contain mature, immature or malignant tissue, possibly in combination [7]. The emergence of a non-germ-cell tumor alongside Germ-Cell Tumor (GCT) is termed as Somatic Malignant Transformation (SMT) [1]. Germ cell tumors with somatic type malignancy are rare, occurring in approximately 2.7% to 8.6% of germ cell tumor cases in adult study [2,8]. Teratoma is the most likely source of the transformed histologies. Several findings support this hypothesis. Teratoma is a pluripotential tissue that can potentially undergo malignant transformation along ectodermal, endodermal, or mesodermal elements, thus explaining the diversity of histologies encountered. This postulate explains our first case. SMT in GCT cannot occur without the dedifferentiation of blastomatous stroma. Dedifferentiation refers to the implantation of a rapidly growing and highly malignant tumor from a slowly growing and well-differentiated neoplasm. Indigenous differentiated cells are transformed or reprogrammed through genetic aberrations or mutations to obtain stemness properties. SMTs can develop in the primary GCT site as well as in metastatic sites [9]. It encompasses a wide variety of histologic subtypes with sarcomas being the most common mainly rhabdomyosarcoma followed by carcinomas and Primitive Neuroectodermal Tumors (PNET) [3].

After platinum-based chemotherapy the incidence of SMT increases up to 14% [10]. The formation of malignant non-germ cell

components following chemotherapy for germ cell malignancies could result from induction of differentiation among the totipotential germ cell (embryonal cell) component of the tumor and/or by malignant transformation of pre-existing teratoma [11]. Usually, SMTs are encountered within the metastatic lesions in late relapses with a history of chemotherapy for the original GCT. This has prompted a hypothesis that SMs may develop from chemoresistant elements of the original GCT. It is believed that chemotherapy mainly affects the more aggressive components of the tumor, while the less aggressive components may later undergo genetic changes and acquire a more malignant potential [12]. Thus, the sarcomatous or neuroectodermal element, although a relatively minor component in the initial specimen, becomes the predominant pattern following successful eradication of the germ cell component by cisplatin-based combination chemotherapy [12]. This postulate explains our second case report, wherein he developed SMT after treatment completion with platinum-based regimen.

Derivation from preexisting neoplasm is further supported by characteristic molecular signatures of GCT in somatic component. Pathogenesis is senescence of cells in slow growing, benign GCT or overgrowth of immature elements. History of GCT may be helpful in testing additional immunohistochemical stains like SALL4, which is an excellent marker for GCT; however, a negative or weakly positive SALL4 staining would not rule out a GCT origin [2]. The finding of isochromosome 12p, a marker of GCT, in most transformed elements arising within GCT, including PNET, supports an origin from a GCT element [3]. This characteristic chromosomal aberration is present in GCT, its various derived tumors, and at both primary and metastatic sites. The presence of i (12p) or 12p gain often means the transition from germ cell neoplasia in situ to an invasive tumor [13].

Diagnostic Criteria

The essential diagnostic criteria of GCT with SMT include the expansile or infiltrative growth of the epithelial or mesenchymal component measuring ≥5 mm. There should be pure population of atypical mesenchymal or epithelial cells and occupy at least one low power field (4× objective). If the overgrowth involves less than one low-power field, it is considered a teratoma rather than SMT [14]. Presence of SM transformation renders worse outcome in comparison to conventional GCT [4]. SMT is generally resistant to chemotherapy targeted at GCT [12]. Stage and feasibility of resection are important prognostic factors. The major challenge in treating these tumors is that the chemotherapy sensitivities of GCT and SM do not overlap. GCT is sensitive to platinum, but SM are not.

Donaldo et al suggested that choice of chemotherapy should be guided on the basis of transformed histology [15]. In our cases, as both of them had PNET transformation, they are on treatment with Ewing sarcoma protocol regimen. Post treatment reassessment with PET scan had shown complete metabolic response in both of them. The three most important favorable prognostic factors, independent by stage and risk category according to the International Germ Cell Cancer Collaborative Group (IGCCCG) classification, are -non-primitive neuroectodermal tumor histology, primary gonadal tumor site, and low number of chemotherapy regimens administered before TMT diagnosis [16]. The type of histology impacts the prognosis. Rhabdomyosarcoma histology is associated with a better prognosis, while PNET is associated with the worst [16]. In terms of prognosis of GCTs with SMs, Sharma et al. observed that patients who had GCT with SMT at first presentation or initial diagnosis had a five-year Overall Survival (OS) rate of 87.5% compared to those who presented with SM in relapse or post-chemotherapy when five-year OS rate dropped to 37-40% [17].

Conclusion

A variety of non-germ cell histologies, including sarcoma, adenocarcinoma, primitive neuroectodermal tumor and leukemia, may occur in association with germ cell tumor. Chromosomal abnormalities in these tumors include isochromosome (12p), reflecting germ cell tumor clonality, these tumors do not respond like germ cell tumor to cisplatin-containing chemotherapy regimens. Treatment should be tailored according to that used in standard management of the transformed histology, and surgical resection is the mainstay of therapy. Hence SMT should be kept in the differential diagnoses' spectrum at the primary setting of GCT when there is poor response to platinum-based regimen or in relapse in context of normal serum markers.

References

1. Spiess PE, Pisters LL, Liu P, Pettaway CA, Kamat AM, Gomez JA, et al. Malignant transformation of testicular teratoma: a chemoresistant phenotype. Urol Oncol. 2008; 26: 595–599.
2. Lutke Holzik MF, Hoekstra HJ, Mulder NH, Suurmeijer AJH, Th Sleijfer D, Gietema JA. Non-germ cell malignancy in residual or recurrent mass after chemotherapy for nonseminomatous testicular germ cell tumor. Ann Surg Oncol. 2003; 10: 131–135.
3. Ulbright TM, Loehrer PJ, Roth LM, Einhorn LH, Williams SD, Clark SA. The development of non-germ cell malignancies within germ cell tumors. A clinicopathologic study of 11 cases. Cancer. 1984; 54: 1824–183.
4. Comiter CV, Kibel AS, Richie JP, Nucci MR, Renshaw AA. Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. J Urol. 1998; 159: 859-63.
5. Spiess PE, Pisters LL, Liu P, Pettaway CA, Kamat AM, Gomez JA, et al. Malignant transformation of testicular teratoma: a chemoresistant phenotype. Urol Oncol. 2008; 26: 595–599.
6. Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma: American Academy of Pediatrics surgical section survey-1973. J Pediatr Surg. 1974; 9: 389–98
7. Mullen M, Rabban J, Frieden IJ. Sacrococcygeal teratoma masquerading as congenital hemangioma. Pediatr Dermatol. 2013; 30: 112–6.
8. Rice KR, Magers MJ, Beck STW, Cary KC, Einhorn LH, Ulbright TM, et al. Management of Germ Cell Tumors with Somatic Type Malignancy: Pathological Features, Prognostic Factors and Survival Outcomes. The Journal of Urology. 2014; 192: 1403-1409.
9. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131: 861–872.
10. Comiter CV, Kibel AS, Richie JP, Nucci MR, Renshaw AA. Prognostic features of teratomas with malignant transformation: a clinicopathological study of 21 cases. J Urol. 1998; 159: 859–863.
11. Michael H, Hull MT, Ulbright TM, Foster RS, Miller KD. Primitive neuroectodermal tumors arising in testicular germ cell neoplasms. Am J Surg Pathol. 1997; 21: 896–904.
12. Umbreit EC, Siddiqui BA, Hwang MJ, Joon AY, Maity T, Westerman ME, et al. Origin of subsequent malignant neoplasms in patients with history of testicular germ cell tumor. Cancers (Basel). 2020; 12: 3755.

13. Bosl GJ, Ilson DH, Rodriguez E, Motzer RJ, Reuter VE, Chaganti RS. Clinical relevance of the i(12p) marker chromosome in germ cell tumors. J Natl Cancer Inst. 1994; 86: 349–355.

14. WHO Classification of Tumours Editorial Board. Urinary and Male Genital Tumours. In: WHO Classification of Tumours. 5th ed, vol 8. International Agency for Research on Cancer 2022. 2023.

15. Donadio AC, Motzer RJ, Bajorin DF, Kantoff PW, Sheinfeld J, Houldsworth J, et al. Chemotherapy for teratoma with malignant transformation. J Clin Oncol. 2003; 21: 4285 91.

16. Giannatempo P, Pond GR, Sonpavde G, Albany C, Loriot Y, Sweeney CJ, et al. Treatment and clinical outcomes of patients with teratoma with somatictype malignant transformation: an International Collaboration. J Urol. 2016; 196: 95–100.

17. Sharma A, Alifrangis C, Milic M, Hall M, Vasdev N, Wilson P, et al. Somatic transformation in metastatic testicular germ cell tumours - a different disease entity. Anticancer Res. 2019; 39: 4911-6.