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Clinicopathological Evaluation of Childhood Sacrococcygeal Germ Cell Tumors: A Single-Center Experience

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What is already known on this topic?

- *Type 1 is the most frequent subtype of sacrococcygeal teratomas.*
- *There is no relationship between tumor size and biological behavior.*
- *It is most frequently observed in the girl, and the most common form is a mature teratoma.*

What does this study add to the topic?

- *As tumor markers, alpha-fetoprotein and beta-human chorionic gonadotropin have been routinely examined clinically and radiologically, along with lesions detected in the sacrococcygeal region.*
- *We recommend routine ultrasonography to patients who come to the clinic with complaints of constipation and inability to urinate.*
- *Type 4 cases are observed more frequently in our series.*

ABSTRACT

Objective: We aimed to evaluate the cases of sacrococcygeal germ cell tumors diagnosed in our hospital between 2006 and June 2021.

Materials and Methods::We evaluated 38 sacrococcygeal germ cell tumors cases in our series in terms of age, sex, clinical complaints, localization, macroscopy, tumor size, histopathological diagnosis, surgical, postoperative complications, treatment, recurrence, and prognosis.

Results: The cases ranged from 1 day to 16 years of age; 14 cases were diagnosed with routine ultrasonographic examination during prenatal period while the rest of the cases most frequently presented with complaints of constipation. In terms of localization, 6 cases were type 1, 11 cases were type 2, 6 cases were type 3, and 15 cases were type 4. In the pathological evaluation, 25 cases were mature teratoma, 8 cases were immature teratoma, and 5 cases were pure yolk-sac tumor. In terms of complications, temporary colostomy was performed as a result of rupture during birth in 2 cases, disseminated intravascular coagulation at birth in 1 case, and colon injury in 2 cases. There was a recurrence in 2 of our cases. Thirty-seven of our cases were alive and 1 died. Alpha-fetoprotein level was high in 28 of our cases.

Conclusion: In our series, type 4 cases were observed more frequently, contrary to the literature. We recommend to use a routine ultrasonography to patients who come to the clinic with complaints of constipation and inability to urinate and if a mass is detected, asking for alpha-fetoprotein for further follow-up. Sacrococcygeal germ cell tumors are ultimately a disease that can be successfully treated with multidisciplinary approach, accurate diagnosis in the antenatal and postnatal period, appropriate surgical intervention, and regular follow-up.

Keywords: Sacrococcygeal germ cell tumor, prenatal, infant, children

INTRODUCTION

Tumors of germ cell origin are lesions located in the gonadal and extragonadal regions and are observed in 1/30000-1/40000 births. Extragonadally, it can be observed in many regions, particularly in the sacrococcygeal region, anterior mediastinum, intracranial, and retroperitoneum. The most common locations of those detected at birth and in the first months are usually the sacrococcygeal region and neck.[1-10]

Although sacrococcygeal teratomas (SCT) are rare, they are the most common fetal neoplasms.[7,11,12] Congenital germ cell tumors originate from the presacral region. Along with the widespread use of ultrasonography (USG) in antenatal follow-up, it has become easy

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to identify SCTs.[7] These tumors are classified into 4 groups according to the Altman classification pursuant to their localization and intrapelvic spread.[13]

Type 1 comprises 46% of the cases and shows mostly external spread, presacral spread is minimal, type 2 comprises 34% of the cases and generally external and intrapelvic spread are close to each other, type 3 comprises 9% of cases and there is mostly pelvic and abdominal spread, while external spread is minimal. Type 4 tumors are completely presacral, and there is no external spread. It comprises 10% of the cases.[13]

Children's Oncology Group developed the following system for staging germ cell tumors: stage I: the tumor has been entirely removed, and tumor markers are normal. Stage II: microscopic traces of the tumor are still present after surgery, tumor markers do not return to normal following surgery. Stage III: visible traces of tumor are left behind after initial treatment and the lymph nodes are affected. Stage IV: the tumor has spread from its original site to other, more distant areas of the body.[5]

Teratomas can be mature, immature, or malignant (teratoma plus 1 or more malignant elements).[8] Treatment is surgical excision of the mass with the coccyx in mature and immature tumors. Surgical approach is usually performed from the sacral region in type 1 and type 2 patients and in the abdominosacral region in type 3 or type 4 patients.[9] In yolk sac tumor, it is recommended to give chemotherapy (bleomycin+etoposide+cisplatin) after surgery.[3] In case of recurrence in mature and immature teratomas, postoperative alpha-fetoprotein (AFP) follow-up, USG examination, and magnetic resonance imaging (MRI) in suspicious cases are recommended after surgery. In yolk-sac tumor, these are recommended after surgery+chemotherapy (CT).

This study aims to evaluate pediatric patients diagnosed with germ cell tumors from the sacrococcygeal region over a 15-year period.

MATERIALS AND METHODS

Thirty-eight cases diagnosed with SCGCT in our hospital between January 2006 and June 2021 were retrospectively analyzed. A 15-year electronic data search was performed in the laboratory information system using the keywords "teratoma or germ cell tumor/yolk sac tumor" plus "sacrococcygeal'' in the diagnostic line. Then patients aged 0-18 years were included in the list. The cases were evaluated in terms of age, sex, clinical admission complaints, localization, macroscopy, tumor size, histopathological diagnosis, surgical, early, and postoperative complications, treatment, recurrence, and prognosis. This study was approved by Başkent University Institutional Review Board (Project No: KA21/298). Since this is a retrospective study, written informed consent was not given by patients for their clinical records to be used in this study.

RESULTS

The ages of the cases ranged from 1 day to 16 years old, 16 (42.1%) cases were under 1 month, 14 (36.8%) cases were between 1 month and 12 months, and 8 (21.1%) cases were over 1 year old. Twenty-four (63.2%) of the cases were girl and 14 (36.8%) were boy. In 14 of the cases, a mass was detected during antenatal (16-30 weeks) USG follow-ups. In the other cases, the most common complaint of coming to the clinic was constipation, inability to urinate, while the lower rate of complaints was swelling, pain, and redness in the suprapubic. In terms of localization, 6 (15.8%) cases were type 1, 11 (28.9%) cases were type 2, 6 (15.8%) cases were type 3, and 15 (39.5%) cases were type 4. Particularly, those with type 3 and type 4 localizations applied to the clinic with constipation and difficulty in urinating. Macroscopically, 17 (44.7%) cases were cystic, 16 (42.1%) cases were solid+cystic, while 3 (7.9%) cases were solid (Table 1). Two cases diagnosed with yolk-sac were first diagnosed with tru-cut biopsy. Tumor size ranged from 1.5 cm to 20 cm, with a mean of 5.75 cm. In our center, samples are processed macroscopically as follows: in cases with a diameter of <5 cm, the entire material is sampled. In cases processed with a diameter >5 cm, at least 1 cassette sample is taken per centimeter. All areas with solid components are sampled. If a suspicious area is observed in the first samples taken, the entire material is sampled.

As a result of the pathological evaluation, 25 (65.7%) cases were mature teratoma, 8 (21.1%) cases were immature teratoma, 5 (13.2%) cases were yolk-sac tumor (Table 2). In 5 of the immature teratoma cases, a mass was detected during the antenatal period and was operated in the first week. All of the yolk-sac cases were diagnosed at the age of 1 year or over. One of the cases was diagnosed in the intrauterine period at an out of center, operated after birth, was diagnosed with mature teratoma, and was out of follow-up at the age of 3 months. Later, when they were 1.5 years old, they applied to our hospital with the complaint of constipation, and the mass was detected in the examinations and they were diagnosed with yolk-sac.

As tumor markers, AFP and beta-human chorionic gonadotropin (B-HCG) have been routinely examined clinically and

Table 1. Summary of Patient's Data

Age, N	Tumour size N
0-28 days, 16 >28 days 1 year, 14 >1 year, 8	1-5 cm, 20 6-10 cm, 9 11-15 cm, 4 16-20 cm, 1 Unknown, 4
Sex Male, 14 Female, 24	Treatment Surgical excision, 33 Surgical excision+CT, 4 Surgical excision+CT+RT, 1
Altmann clasification Type 1, 6 Type 2, 11 Type 3, 6 Type 4, 15	Diagnosis Mature teratoma, 25 Immature teratoma, 8 Yolk-sac tumor, 5
Complications Tumor rupture, 2 Colon injury, 2 DIC, 1 Recurrence, 2 Mortality, 1	Surgical approach Sacral approach, 17 Abdominosacral, 21

CT, chemotherapy; RT, radiotherapy; DIC, disseminated intravascular coagulation.

Table 2. Features of Immature Teratoma and Yolk-Sac Cases

Case	Age at Diagnosis	Sex	Diagnosis	Type	Tumour Size	Treatment	Prognosis	Complaint
1	5	Female	Yolk-sac	4	3.5 cm	Surgical+CT	Alive	Hydronephrosis, constipation, inability to urinate
2	1.5	Male	Yolk-sac	3	Tru-cut	Surgical+CT	Alive	Constipation
3	1	Male	Yolk-sac	4	2 cm	Surgical+CT	Alive	Inability to urinate
4	1	Female	Yolk-sac	4	Tru-cut	Surgical+CT	Alive	Constipation, inability to urinate
5	1	Female	Yolk-sac	4	8 cm	Surgical+CT+ RT	Ex	Constipation
6	6 days	Female	Immature teratoma	2	7 cm	Surgical	Alive	Supraubic mass
7	1 day	Female	Immature teratoma	3	5 cm	Surgical	Alive	Intrauterine mass
8	1 day	Female	Immature teratoma	2	15 cm	Surgical	Alive	Intrauterine mass
9	1 day	Female	Immature teratoma	2	5 cm	Surgical	Alive	Intrauterine mass
10	1 day	Male	Immature teratoma	2	15 cm	Surgical	Alive	Intrauterine mass
11	1 day	Female	Immature teratoma	1	Ready block	Surgical	Alive	Intrauterine mass
12	6 months	Female	Immature teratoma	4	2 cm	Surgical	Alive	Constipation, inability to urinate
13	4 months	Male	Immature teratoma	2	Ready block	Surgical	Alive	Supraubic mass

CT, chemotherapy; RT, radiotherapy.

radiologically, along with lesions detected in the sacrococcygeal region. Due regard was given to physiologically raised levels of AFP in this age group (Table 3).[14] While AFP level is high in 28 of our cases, it is observed at normal levels in post-treatment follow-ups (Table 4). Three of our cases had elevated B-HCG at the time of diagnosis (case 1: 1-month-old, girl, mature teratoma, 38.60; case 2: 2-day-old boy, mature teratoma, 29.70; case 3: 2-day-old girl, mature teratoma, 62.30). The range of 0-2.5 ng/mL is considered normal for the B-HCG level. The primary tumor was surgically resected with the coccyx in all cases. In accordance with the literature, the surgical approach is generally performed from the sacral region in type 1 and type 2 patients and from the abdominosacral region in type 3 or type 4 patients. Two of our yolk-sac cases were diagnosed with tru-cut biopsy first, and surgical excision was performed after neoadjuvant 6 cures of CT, and complete response to treatment was observed in both cases. One of the other 3 cases was operated in out of center and diagnosed, and the other 2 cases received surgical excision first and then CT. In terms of chemotherapy protocol in our hospital, bleomycin+etoposide+cisplatin combination is applied. One of the yolk-sac cases had bone, lung, and liver metastases at the time of diagnosis, 1 had lung metastasis, and the other had liver metastasis.

One of our patients had scoliosis, butterfly vertebra, atrial septal defect (ASD), ventricular septal defect (VSD), and hearing loss as well as teratoma, 1 had anal atresia and patent ductus arteriosus (PDA), and 3 had anal atresia.

Our cases diagnosed in the intrauterine period were delivered by cesarean, and 2 cases (20 cm and 15 cm in size) had rupture during birth, while disseminated intravascular coagulation (DIC) developed in 1 case. Colostomy was performed temporarily in 2 of our type 4 cases due to colon injury.

The cases are in our follow-up and are being followed up in remission. Thirty-seven of our cases were alive and 1 died. Our case, who died, was diagnosed out of center and came to our department as a ready-made paraffin block and was diagnosed as yolk-sac tumor in our department, and lung metastasis was present at the time of diagnosis. They received CT and radiotherapy and died after 22 months.

DISCUSSION

Germ cell tumors are rare tumors that makes up only 4% all cancers in children. Teratomas are the most common in this group.[5] Teratomas are neoplasms that contain tissues originating from all 3 germ layers of the embryo.[8] It is observed 2-4 times more frequently in girls than in boys.[6,8] In our series, the girl/boy rate was 1.7/1. Sacrococcygeal germ cell tumors are mean 8 cm and range from 1 cm to 35 cm. There is no relationship between tumor size and biological behaviour.[10,15] Tumor size in our series ranged between 1.5 cm and 20 cm, with a mean of 5.75 cm. The mean of mature teratomas was 5.3, immature ones were 7 cm, while yolk-sac had a mean of 4.8, and no correlation was observed between tumor size and behavior.

Sacrococcygeal teratomas are generally large, unencapsulated masses with cystic and solid areas. Most of the teratomas

Table 3. Serum Alpha-Fetoprotein Levels in Normal Infants (reference 14).

Age	Mean ± SD, ng/mL
Premature	134 734 ± 41 444
Newborn	48 406 ± 34 718
Newborn-2 weeks	33 113 ± 32 503
2 weeks-1 month	9452 ± 12 610
1 month	2654 ± 3080
2 month	323 ± 278
3 month	88 ± 87
4 month	74 ± 56
5 month	46.5 ± 19
6 month	12.5 ± 9.8
7 month	9.7 ± 7.1
8 month	8.5 ± 5.5
>8 month	8.5 ± 5.5

in our series were observed as cystic. Sacrococcygeal germ cell tumors are rare tumors and are mostly diagnosed in the prenatal period or within a few days after birth, while 10% are diagnosed after 2 years.[16] While 14 (36.8%) of our cases were diagnosed during antenatal period, 8 (21.1%) of our cases were diagnosed after the age of 1. Sacrococcygeal germ cell tumors are generally benign lesions. However, perinatal morbidity and mortality are high in patients due to heart failure, premature birth, polyhydramnios, anemia, and tumor rupture.[3,8,17] It is mostly benign in the neonatal period and the risk of malignancy increases within months. While the risk is 7%-10% in the first 2 months, 20% at the end of the second month, and it increases to 37% around the age of 1. Hence, complete resection of the mass with the coccyx as soon as possible is recommended.[9,17] While approximately 80% of all teratomas are benign, 20% have malignant characteristics.[18]

While SCTs are more easily recognized by USG, particularly type 1 and type 2, the diagnosis is more difficult in type 3 and type 4, whose tumor density is mostly intrapelvic due to acoustic shadowing in the bony pelvis.[8] Magnetic resonance imaging is very useful for accurate evaluation in these situations.[8]

Recurrences are observed in an average of 10% (0%-26%) after resection of mature teratomas. While it is significantly higher in immature teratomas (12%-55%, mean 33%), it is observed at an mean rate of 18% (0%-36%) in malignant teratomas.[8] This rate can be attributed to the successful treatment of malignant teratomas with combined CTs. Since recurrences are generally within 3 years in SCTs, close follow-up and follow-up of AFP are recommended for 3 years with 3-month intervals.[19]

Recurrence was observed in 2 cases in our series. One of them was a case who was diagnosed at birth at out of center and was diagnosed with mature teratoma, came out of follow-up after 3 months, and was admitted to our hospital with the complaint of constipation when they were 1.5 years old, and a mass was detected during the examinations and was diagnosed with yolk sac. Although the first examples of the case were not sampled by us, we think that it may be a mixed germ cell tumor in the first place. The other was a case who was diagnosed with meningomyelocele at out of center and then admitted to our hospital at the age of 3 with the complaint of constipation, and a mass was detected while examinating and was diagnosed with mature teratoma.

Sacrococcygeal teratomas are accompanied by congenital malformations at a rate of 5%-26%. Anorectal, genitourinary, and vertebral malformations are the most common accompanying malformations.[10,20] Besides, it may accompany anomalies such as sacral agenesis, meningocele, cardiac anomalies, gastrointestinal anomalies, imperforate anus, and anal atresia.[10] Hemivertebra, butterfly vertebra, scoliosis, ASD, and VSD were accompanied by hearing loss in 1 of our cases (8 months,

Table 4. Alpha-Fetoprotein Values of the Cases During and After Diagnosis

	Diagnosis	AFP (at the Time of Diagnosis)	AFP (Mid Control)	AFP (Latest)
1	MT	159.054	42.626	1.906
2	MT	924.713	274.775	29.093
3	MT	2.054	-	-
4	MT	236.80	117.342	2.67
5	MT	367.83	57.745	2.71
6	MT	776.70	400.20	3.00
7	MT	5.70	3.40	1.60
8	MT	1.3	2.40	2.70
9	MT	6.80	6.57	0.98
10	MT	60.007	37.153	114.73
11	MT	172.504	37.005	1.106
12	MT	2.84	3.65	1.71
13	MT	697.38	102.62	5.66
14	MT	145.65	34.62	2.80
15	MT	1.14	-	-
16	MT	525.80	117.90	1.26
17	MT	3.65	3.46	2.37
18	IT	>1.000.00	1.187.30	10.20
19	YCT	>1.000.00	2.590.80	34.384
20	YCT	159.012	131.32	13.60
21	IT	949.75	801.00	68.20
22	IT	>1.000.00	825.73	3.03
23	IT	>1.000.00	42.861	2.87
24	IT	>1.000.00	645.74	2.23
25	YCT	-	-	2.43
26	IT	-	-	3.46
27	IT	>1.000.00	912.64	4.32
28	MT	173.56	64.87	2.48
29	MT	428.67	114.56	2.61
30	YCT	>1.000-00	1.215-46	1.37
31	YCT	>1.000.00	-	3.6
32	MT	6.2	4.7	2.12
33	IT	-	-	4.76
34	MT	3.45	-	-
35	MT	135.12	43.87	2.31
36	MT	6.54	4.2	-
37	MT	80.87	35.98	1.67
38	MT	117.89	69.08	3.08

MT, mature teratoma; IT, immature teratoma; YCT, yolk-sac tumor; AFP, alpha-fetoprotein.

boy, type 4, mature teratoma). Our another case (3 years old, girl, mature teratoma, type 4) underwent a meningomyolesal operation on the postnatal first day. After 3 years, a mass with a diameter of 2.5 cm is detected in the sacral region while being investigated due to constipation and difficulty in urination. Four of our patients had anal atresia, and 1 of our patients also had PDA.

The most significant factors affecting the prognosis of congenital SCT are gestational age, tumor size, total resection of the mass, and its histopathological content.[21,22] Generally, the diagnosis is made by USG in the prenatal period.[1,2,21] However, diagnosis may be delayed until complaints due to urinary or intestinal obstruction, particularly in patients with type 3 and type 4 tumors.[23,24] In terms of localization, type 1 is most frequently observed, while type 3 and type 4 are observed less frequently. However, type 4 is the most common in our series. This may be due to the fact that our hospital is a developed center in terms of consultation and the mass is detected as a result of detailed examination of cases with constipation and inability to urinate. Ultrasonography and MRI in suspicious cases are performed in our routine. When the mass is detected radiologically, AFP and B-HCG are routinely checked. It is very significant to evaluate AFP levels in terms of recurrence and metastasis follow-up during diagnosis and follow-up of teratomas.[6] In our hospital, AFP level is first checked weekly after the operation until it returns to normal, for the following year, particularly in patients receiving CT, it is checked monthly, and follow-ups are checked every 3 months. In mature and immature teratomas, on the other hand, after returning to normal, they are examined every 3 months for the first year and every 6 months for the next 3 years.

The anatomical proximity of the sacral region with the pelvic organs, the size of the mass, uncontrollable intraoperative hemorrhages, incomplete resection of the mass, high recurrence rates, and neurological dysfunctions are the difficulties encountered by surgery.[9]

Hemorrhagic complications are the most common cause of death during surgical resection in the neonatal period.[25,26] Disseminated intravascular coagulation developed in 1 of our cases after surgery. Another complication is injuries to the colon, ureter, and bladder during surgery, particularly in type 4 cases.[6,27] In our series, 2 patients had colon injuries and colostomy was performed.

Another complication is tumor rupture. Due to the risk of rupture during birth, cesarean delivery is recommended, particularly in cases with a tumor diameter of 5 cm or more detected by USG during antenatal period.[6,7] Cesarean delivery was performed in our cases diagnosed during antenatal period, and 2 cases with tumor size of 15 cm and 20 cm had tumor rupture.

As SCGCT is extremely rare, there are no clear medical diagnosis and treatment guidelines yet. While SCGCT was diagnosed in the postnatal period before the routine application of prenatal USG, it is now seen in the prenatal period with the increase of cases diagnosed in the intrauterine period and since it is also seen in advanced ages, it is a disease with a multimodal treatment step that concerns many departments including obstetrics, neonatal, pediatric surgery, general pediatrics, pathology, radiology, and pediatric oncology. By creating medical guidelines, the disease concept, diagnostic criteria, and severity assessment can help make follow-up decisions for prenatal management, treatment, and patient families and general practitioners, including obstetricians, neonatologists, pediatricians, and pediatric surgeons. Sacrococcygeal teratomas are ultimately a disease that can be successfully treated with a multidisciplinary team approach, accurate diagnosis in the antenatal and postnatal period, appropriate surgical intervention, and regular follow-up.

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (Approval No: KA21/298).

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