Emergence of Ectopic Adrenal Tissues-What are the Probable Mechanisms?

 Gürkan Tarçın, Oya Ercan

İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey

Abstract

Ectopic adrenal tissue, defined as the formation of adrenal tissue in an abnormal anatomical location, is not a rare entity and may have clinical significance. Even though the mechanism for their emergence has not been fully understood, numerous cases of ectopic adrenal tissue have been reported, mostly in the vicinity of the original location of adrenal gland, such as in kidneys and gonads. In these cases, most authors attributed their emergence to a probable migration defect. However, this mechanism does not simply explain the ectopic tissues in remote locations, such as in the hypophysis or lungs. This review summarizes these reports, describing many different locations in which ectopic adrenal tissues were encountered, together with their suggested mechanisms.

Keywords: Ectopic adrenal, adrenocortical, heterotopia, choristoma, adrenal rest

Introduction

Embryogenesis begins with a single cell, a newly fertilized oocyte. This cell is totipotent, that is it is capable of giving rise to many different types of tissues, even extraembryonic tissues, such as placenta, under certain physiological conditions. During development from zygote to a multicellular organism, cells are permanently in communication with their neighbor cells, sending and receiving molecular signals. Several intracellular signaling pathways have been elucidated, such as the fibroblast growth factor, sonic hedgehog and wingless pathways. These signaling mechanisms enable the cells to go through an intricate series of events: proliferation, cell fate determination, survival, differentiation, apoptosis, migration, adhesion and cell shape changes (1,2). After the proliferation phase, cells are predisposed to their particular fate and acquire characteristics of different cell lineages and subsequently migrate to their appropriate locations within the embryo. Defects in migration at all stages of development may cause severe conditions (3).

The terms "ectopia" and "heterotopia" are used interchangeably, and ectopic tissues may also be called "accessory" or "rest" tissues. They all refer to the presence of a mature tissue within another tissue due to a developmental anomaly, which occurs when fragments of the tissue split off and move to n inappropraite area or due to an incomplete separation of the tissue from the adjacent organs during development. If heterotopic tissues aggregate and form a tumor-like mass, it is called a "choristoma", as the suffix "-oma" is added to indicate a tumor (4,5). Morgagni, who noticed "yellowish nodules with the characteristics of adrenal tissue in the near vicinity of the gland" was the first to report heterotopic adrenal tissue in 1740 (6). Approximately 150 years later, Marchand (7) encountered adrenal tissue remnants in fetal and infant cadavers, and speculated that adrenal cells could adhere to neighboring tissues and thereby migrate to an abnormal location during early stages of embryogenesis.

Adrenogenital Development

To better understand the mechanism of emergence of ectopic adrenal tissues, it is necessary to also understand adrenogenital development. The adrenal gland has a dual embryological origin as it consists of two parts: cortex and medulla, arising from the intermediate mesoderm and neural crest cells, respectively. The adrenogonadal primordium appears as a thickening of the coelomic

Address for Correspondence: Oya Ercan MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Pediatric Endocrinology, İstanbul, Turkey
Phone: + 90 212 414 30 00 **E-mail:** oyaercan1@gmail.com **ORCID:** orcid.org/0000-0001-7397-2837

epithelium from about 4 weeks post conception (wpc). Adrenogenital primordium separates from the epithelium and invade the underlying mesenchymal layer of the intermediate mesoderm. The cells next to the mesonephros migrate dorsolaterally to form the gonadal primordium, while the more medial cells migrate dorsomedially to form adrenal primordium at 33 days post conception (dpc). Meanwhile, adrenal medulla begins to develop from the neural crest. From 6 wpc, neural crest cells, which differentiate into chromaffin cells, migrate towards and enter the developing adrenal primordium (Figure 1). By 50-52 dpc, the inner fetal zone, forming the major part, and the outer definitive zone are detectable in the adrenal cortex. By 9 wpc, the adrenal gland is encapsulated and intensely vascularized with subcapsular arteriolar plexus. At this time, the gland contains a cortex containing the definitive zone and fetal zone and a center containing islands of chromaffin cells. A third cortical zone, the transitional zone, found between the definitive zone and the fetal zone, appears by 14 wpc. Subsequently, the fetal zone begins to involute and the definitive zone and transitional zone give rise to the zona glomerulosa and zona fasciculata, respectively, which mature under the stimulation of adrenocorticotropic hormone (ACTH) and angiotensin (8,9,10).

Ectopic Adrenal Tissues Contain Either Cortex Only or Both Cortex and Medulla

Adrenal rest tissues may contain only cortex or both cortex and medulla, depending on whether the fragments separate before or after medullary tissue migrates into the cortex (5). As mentioned earlier, the adrenal gland, particularly the cortex, has an anatomically close relation to the gonads during embryogenesis. Therefore, it has been postulated that adrenal rests may descend together with the testes in males in the embryological period and contain only cortex, while the adrenal rests close to the normal location of the adrenal gland may also contain medulla. This process has been suggested for and is commonly accepted as the etiology of testicular adrenal rest tumors (5,11).

As for the ectopia of adrenal medulla, chromaffin cells of the adrenal medulla and sympathetic neurons were thought to derive from common neural crest precursors until recently (12). However, recent studies have shown that "Schwann cell precursors" (descendants of the neural crest) directly give rise to adrenal medulla (13). Also, chromaffin cells of the adrenal medulla differ from extra-adrenal chromaffin cells in regard to their "molecular cross-talk" with the steroidogenic cells of the adrenal cortex. This interaction between adrenal chromaffin cells and cortex is essential for the maturation of adrenal medulla, whereas the Zuckerkandl organ, the largest extra-adrenal chromaffin accumulation in mammals, lacks such interaction with steroidogenic tissue and undergoes involution after birth (postnatal autophagy-mediated cell death) in the absence of cortex-derived glucocorticoids (14). This appears to be the reason for the absence of literature describing ectopia of adrenal medulla only, that is not surrounded by cortex, while entities related to adrenal or extra-adrenal chromaffin cells (pheochromocytoma and paraganglioma), and even pheochromocytoma in ectopic adrenal gland have been reported (15,16).

Probable Impact of Adrenocorticotropic Hormone Levels on the Emergence of Ectopic Adrenal Tissues

Adrenocortical rests are commonly found in children in the retroperitoneal area, appearing as bright-yellow nodules. These tissues are present in approximately half of the newborns and generally undergo atrophy and disappear within several weeks after birth. In some cases adrenocortical rests may also undergo hyperplasia under excess stimulation of increased ACTH secretion, which may even give rise to a neoplasm. The latter mechanism has been suggested in the pathogenesis of testicular adrenal rest tumors in patients with congenital adrenal hyperplasia, and it also explains the higher prevalence of testicular adrenal rests in this patient group (up to 94%) than in healthy newborns (7.5-15%) based on autopsy and surgical findings (17,18). A glucocorticoid replacement regimen for congenital adrenal hyperplasia is useful in the treatment by suppressing ACTH secretion and thereby regulating excess androgen secretion (19).

Suppressing ACTH levels with glucocorticoid replacement has been reported to lead to a reduction in testicular
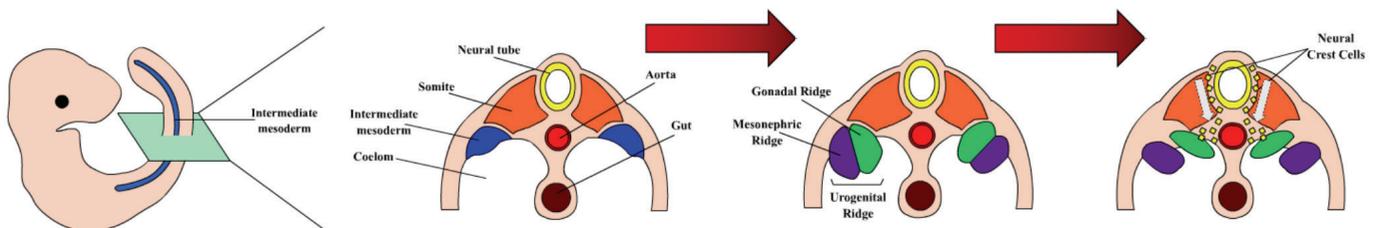
Figure 1. Development of the adrenal cortex and the migration of the neural crest cells to form the adrenal medulla

adrenal rest tumor size and improve testicular functions. Concordantly, the prevalence of testicular adrenal rest tumors is higher in patients with severe forms of congenital adrenal hyperplasia who are exposed to higher ACTH levels, even *in utero*, than those with non-classic congenital adrenal hyperplasia with moderate elevation of ACTH, given the fact that ACTH receptors are found in testicular adrenal rest tumor tissues (20).

There are a number of studies and observations supporting the role of ACTH in the development of testicular adrenal rest tumors in patients with congenital adrenal hyperplasia. As with conditions in which patients are exposed to high levels of ACTH from early infancy, adrenal rest tumors have occasionally been reported in Nelson's disease (Table 1) which is an acquired condition in later years of life associated with high levels of ACTH (20).

ACTH plays a crucial role both in the development of adrenal glands and in the regulation of cell differentiation (8). This effect of ACTH on adrenal glands has also been demonstrated in animal research with 12-week-old mice. After an injection of tetracosactide, a synthetic peptide analogue of ACTH, cell proliferation was observed in adrenal zonae glomerulosa and fasciculata of mice, which was consistent with the hypothesis that adrenal cortex may contain progenitor or slow-cycling stem cells, activated by the stimulus of ACTH (21).

High levels of ACTH seem to be a prominent factor for the emergence of adrenal rest tumors. However, these tumors are also found in patients having adequate glucocorticoid replacement and thus have normal levels of ACTH, suggesting that ACTH level is not the only factor involved (22).

Recent Speculation About Other Possible Stimulating Factors

In recent years, more detailed studies on the origin and characteristics of adrenal rest tumors have demonstrated that these tumors also have Leydig cell characteristics (expression of *INSL3*, *LHCGR* and *HSD17B3* genes) and receptors for angiotensin II and luteinizing hormone, as well as for ACTH. Therefore, it has been hypothesized that these tumors have an origin from a pluripotent cell type, probably from the urogenital ridge or the adrenogonadal primordium, and other factors, such as angiotensin 2 and luteinizing hormone may be involved as well (11,20,22,23,24).

Defects During the Migration of Precursor Cells

Given that adrenocortical rests are thought to be derived from the urogenital ridge or the adrenogonadal primordium, it is not surprising that these tissues can be found anywhere along the migratory course of the gonads, the descending path of testes and in the vicinity of the kidneys and adrenal glands. Sullivan et al. (25) conducted a study in children under the age of 16 years reporting that in 25 out of 935 groin explorations performed due to various surgical conditions, such as inguinal hernia, undescended testis or hydrocele, adrenocortical tissues were found incidentally in 2.7%. The absence of adrecortical tissue in any of the 35 girls involved in this study supports the idea that adrenocortical tissue fragments may be scattered along the path during the descent of the testes. On the other hand, gonadal adrenal rests are also reported in females in one or both ovaries, broad ligament (26) and fallopian tube (27), though it is rare. These cases were described in adult female patients presenting with heavy menstrual bleeding, dysmenorrhea, progressive

Table 1. Gonadal masses in patients with Nelson's disease reported in the literature						
Reference	Gender	Age at diagnosis of Cushing's syndrome	Age at surgery and surgical approach	Interval between surgery and development of ND	Age at diagnosis of the tumor	Location of the tumor
Hamwi et al. (48), 1964	M	7 yrs	7 yrs, left total and right subtotal adrenalectomy	1 yr	14 yrs	Left testicle
Baranetsky et al. (49), 1979	F	24 yrs	24 yrs, bilateral adrenalectomy	1 yr	35 yrs	Bilateral paraovarian
Johnson and Scheithauer (50), 1981	M	15 yrs	15 yrs, bilateral adrenalectomy	1 yr	23 yrs	Both testicles and left spermatic cord
Verdonk et al. (51), 1981	F	25 yrs	25 yrs, bilateral adrenalectomy	24 yrs	49 yrs	Bilateral paraovarian and broad ligament
Ntalles et al. (52), 1996	M	19 yrs	23 yrs, bilateral adrenalectomy	1 yr	29 yrs	Both testicles
Puar et al. (24), 2016	M	11 yrs	15 yrs, bilateral adrenalectomy	1 yr	27 yrs	Bilateral testes

ND: Nelson's disease, yrs: years, yr: year, M: male, F: female

abdominal distension, abnormal menstruations and/or menorrhagia (26).

Besides gonadal adrenocortical rests, there are a few case reports describing adrenocortical tissues in the renal hilum (28,29). Both the kidneys and the adrenal cortex arise from mesenchymal tissue, and develop in the pelvis. As the kidneys migrate upwards to the upper lumbar region, they meet the adrenal tissue at 8 wpc. This interaction may explain the underlying mechanism of the adrenocortical tissues in the renal hilum (Figure 2). However, apart from these locations, atypically located adrenal rests (i.e. lungs, hypophysis, spinal canal etc.), the mechanisms of which are more difficult to explain, have also been reported in the literature (5).

Hypotheses Concerning the Impact of Steroidogenic Factor-1 (NR5A1) Overexpression

In the early 1900s, steroidogenic factor-1 (SF-1) was first identified as a key regulator of steroidogenic enzymes (30). Later, SF-1 was shown to control endocrine development and function, as it is expressed in the adrenal gland, gonads, pituitary gonadotroph cells and ventromedial hypothalamus.

During embryogenesis, the adrenogonadal primordium is identified by its expression of SF-1. Thereafter, the fate of the bipotential precursor cells is determined by their SF-1 expression levels. The cells expressing higher levels of SF-1 form the adrenal primordium, while those expressing lower levels form gonadal primordium (10).

Based on mouse models, deletion of the gene encoding SF-1 was shown to cause agenesis, delayed or incomplete development of the adrenal glands, gonadal dysgenesis, abnormalities of the ventro-medial hypothalamus and partial hypogonadotropic hypogonadism, while overexpression of SF-1 has been shown to cause increased proliferation and decreased apoptosis of the adrenocortical cells, resulting in aberrant proliferation and neoplasia in the adrenal tissue (8,31).

A fetal adrenal enhancer (FaDE) which initiates SF-1 expression has been identified and demonstrated to be activated in gonads, adrenal cortex and, interestingly, in the thorax (32). In a later study conducted with transgenic mice by the same researchers, SF-1 was overexpressed using a FaDE-SF-1 transgene, and in addition to increased adrenal size, emergence of ectopic adrenocortical cells in the thorax expressing steroidogenic markers, including CYP21, was observed. This finding may help explain the few cases of adrenocortical tissues in the thorax. The same study also revealed that in these transgenic mice, gonads remained adjacent to the kidneys. The researchers speculated that emergence of the ectopic adrenal tissue in the inguinoscrotal region resulting from the overexpression of SF-1 could interrupt the separation of the gonads, and attributed this to the frequent accompaniment of cryptorchidism with ectopic adrenal tissue in boys (33).

Adrenal Rests in the Hypophysis and the Link to SF-1

At the time of writing, five cases of corticotroph adenoma with interspersed adrenocortical cells have been reported (34,35,36,37,38). Of these, four cases were in the pediatric age group. In Table 2, the characteristics and suggested pathogenesis causing ectopia are summarized. Although in three of these cases, the underlying pathogenesis of the misplaced adrenocortical cells was attributed to a migration defect during embryogenesis, the location of the choristoma in the hypophysis is quite distant from those ectopic tissues reported to be in the vicinity of the adrenal gland (35,36,38). Thus, its emergence in the hypophysis is unlikely to stem from a migration defect. As another proposed mechanism, the emergence of the adrenocortical cells interspersed with corticotroph cells was attributed to a possible paracrine mechanism. It was suggested that the corticotroph cells were able to stimulate and convert the neighboring cells to adrenocortical cells (34,37). However, in only one of the five cases (37), corticotroph adenoma was found to be functional (i.e., it had endocrine activity). The most remarkable mechanism was suggested by Mete
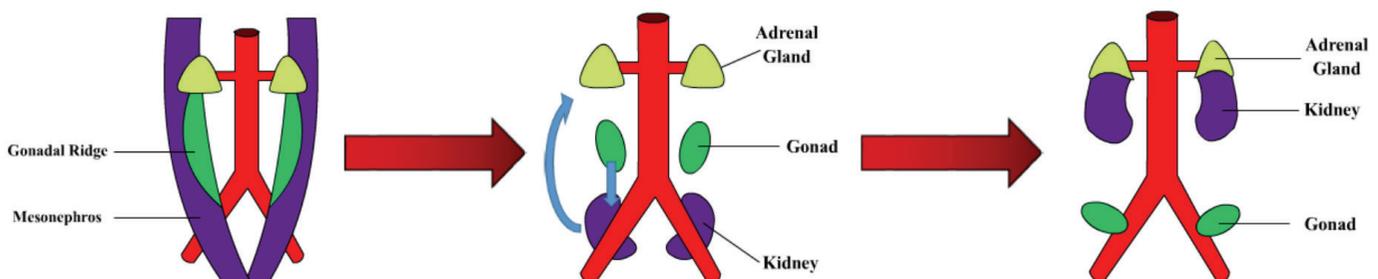
Figure 2. Interaction among the adrenal glands, kidneys and gonads during embryogenesis

et al. (36) in 2013, highlighting a common feature between the adrenal and pituitary glands, namely SF-1, which has an important role in the development of the both glands.

SF-1 is a common key molecule in the differentiation of both gonadotropic cells in the hypophysis and adrenocortical cells. Also, in case of SF-1 overexpression, emergence of adrenocortical tissue may be expected, as described earlier. However, the relevant study (33) does not mention a generation of adrenal ectopia in the pituitary region. Also, in addition to SF-1, several other essential regulators, such as Prophet of Pit1 (Prop1), Homeobox protein ANF (HesX1) and Lhx3, play a significant role in the differentiation of gonadotrophs in the hypophysis (39), and differentiation of adrenocortical cells is also dependent on several other regulators, such as DAX1, corticotropin-releasing hormone, ACTH and WT1 (40). Therefore, the hypothesis about an isolated effect of SF-1 appears to be insufficient to explain an erroneous emergence of adrenocortical cells in the hypophysis.

Unusual Locations of Adrenal Rest Tissues and Proposed Mechanisms

Adrenal rest tissues have also been reported in many places other than the above-mentioned organs, such as in the lung, mediastinum, gastric wall, liver, placenta and spinal canal. While some authors suggested a possible mechanism to explain the abnormal locations of these tissues, others either supported these hypotheses or did not present an opinion at all. The characteristics of the cases and the suggested pathogeneses for the presence of adrenal rest tissues in these abnormal locations are shown in Table 3.

The adrenal rest tissues of all the cases listed in Table 3 involve only cortex, except for the paratracheal 5-mm lesion reported by Shigematsu et al. (41) which contained both cortical and medullary features. Only in three cases adrenal rest tissues were reported to be clinically functional. Two cases presented with signs of virilization (42,43) and one case with Cushingoid appearance (44).

When Table 3 is examined in detail, a few points emerge. In 3 out of 4 cases with adrenal rest tissues located in the placenta, it is noteworthy that the births were premature, and one of the cases had intrauterine growth retardation in addition to being premature. However, the authors did not state if the preterm births could be related to the lesion in the placenta. Only Cox and Chavrier (45) stated that adrenocortical tissue was unlikely to be responsible for intrauterine growth retardation in their report of a late preterm neonate with intrauterine growth retardation. In all the cases of hepatic adrenal rest tissue, the tumors were found in the posterosuperior segment of the right hepatic lobe. As some of the authors of these reports mentioned, hepatocellular carcinomas and adrenal rest tumors cannot be differentiated without an immunohistochemical analysis due to their histological similarity. Therefore, it was suggested that adrenal rest tissues should be considered in the differential diagnosis of the tumors, especially those located in subsegment 7, and immunohistochemical analyses should be performed (46).

Spinal canal is another location where a number of cases of adrenal rest tissues have been reported. Most of the cases were with extramedullary involvement, and presenting symptoms appear to be related to spinal cord compression, such as weakness and/or pain in the legs, lumbar pain or symptoms associated with urination, depending on the affected level of the spine. The access of the adrenal tissue to the spinal canal was suggested to be via the sheath of an exiting nerve or the adventitia of an in-growing segmental lumbar artery of the aorta (47).

Clinical Features of Adrenal Rest Tissues

Adrenal rest tissues, even if found incidentally in most of the cases, may be symptomatic due to mass effect, as in the case of the spinal canal location. This effect has a

Table 2. Adrenocortical cells reported within the pituitary gland

Reference	Age/gender	Presenting complaint	Tumor size	Suggested pathogenesis
Oka et al. (34), 1996	16/M	Growth retardation	15 mm	Possible paracrine effect between two cell types
Coiré et al. (38), 1998	18/F	Amenorrhea	13 mm	Abnormal differentiation of a stem cell or misplaced adrenocortical cells during embryogenesis
Albuquerque et al. (37), 1999	16/M	Delayed growth	17.5 mm	Possible paracrine interaction
Mete et al. (36), 2013	35/M	Headache	N/D	Abnormal differentiation of a stem cell which might be related to SF-1
Turan et al. (35), 2021	11/M	None, incidental finding on MRI during investigation of central hypothyroidism	11 mm	Abnormal differentiation of a stem cell or misplaced adrenocortical cells during embryogenesis

MRI: magnetic resonance imaging, SF-1: steroidogenic factor-1, M: male, F: female, N/D: Not determined

Table 3. The characteristics of the cases and the suggested pathogeneses for the presence of adrenal rest tissues in other abnormal locations

Reference	Age/gender	Presenting complaint	Location/size	Suggested pathogenesis
Bozic (53), 1974	2-day-old/F	Mild cyanosis after birth (death on the second day)	Superior lobe of the right lung	Misplaced mesothelial cells. As the pleura and adrenal glands have the same mesodermal origin, pleural mesothelium may give rise to ectopic adrenocortical tissue.
Armin and Castelli (54), 1983	5-day-old/M	Meningitis and midbrain hemorrhage, death on the fifth day	Lung, two nodules measuring 0.5 cm	N/D (Bozic's hypothesis was supported)
Shigematsu et al. (41), 2007	99 year-old/F	Respiratory disturbance, high fever (Pneumonia)	Paratracheal region/5 mm	Primitive mesothelium and chromophil cells might be incorporated into the ectopic adrenal tissue in the thorax by an unknown mechanism.
Medeiros et al. (42), 1992	44-year-old/F	Signs of virilization	Mediastinum, in contact with the pericardium/6x5x3.5 cm	N/A
Ren et al. (55), 2013	72 year-old/F	Upper abdominal discomfort, nausea	Lesser curvature side of the gastric antrum/15x25 mm	Due to the malposition or self-differentiation of mesothelial cells during the embryonic period.
Wallace et al. (43), 1981	23 year-old/F	Amenorrhea, signs of virilization	Entire right lobe and partially left lobe of the liver/18x15x15 cm	N/A
Contreras et al. (44), 1985	21/F	Cushing appearance	Posterosuperior subsegment of the right hepatic lobe/4 cm	N/A
Arai et al. (56), 2000	62/M	None, detected in USG performed for chronic HCV infection	Posterosuperior subsegment of the right lobe of the liver/25x18x15 mm	N/A
Tajima et al. (57), 2001	55 year-old/F	None, incidentally detected in USG during routine medical check-up	Posterosuperior subsegment of the right hepatic lobe/2.5 cm	Derived from adrenal primordium migrating to neighboring organs
Baba et al. (58), 2008	67 year-old/F	None, incidentally detected in USG during routine medical check-up	Posterosuperior subsegment of the right hepatic lobe/17x14x11 mm	Derived from adrenal primordium migrating to neighboring organs
Shin (59), 2010	62 year-old/M	None, incidentally detected in USG during routine medical check-up	Posterosuperior subsegment of the right hepatic lobe/3 cm	N/A
Soo et al. (60), 2014	47 year-old/F	Elevation of aminotransferases	Segment 7 of the liver/3.4 cm	N/A
Valle et al. (61), 2014	58 year-old/M	None, found in USG perfomed for HIV and HBV coinfection	Segment 7 of the liver/25 mm	N/A
Sugiyama et al. (46), 2015	50 year-old/F	Incidentally detected in CT performed for uterine leiomyoma	Segment 7 of the liver/2x3 cm	N/A
Enjoji et al. (62), 2017	67 year-old/F	None, detected in USG performed for elevated GGT	Segment 7 of the liver/17 mm	Misplaced mesothelial cells or autonomous differentiation of mesodermal elements
Cox and Chavrier (45), 1980	27 year-old/F	Preterm birth, intrauterine growth retardation	Placenta	During embryogenesis portion of the coelomic mesenchyme migrated, or went astray, and finally became integrated with the extracoelomic mesenchyme within the placenta.
Qureshi and Jacques (63), 1995	30 year-old/F	Preterm birth, fetal distress,	Placenta	Supported the hypothesis of Cox and Chavrier (45)
	39 year-old/F	Spontaneous rupture of membranes	Placenta	
Guschmann et al. (64), 1999	29 year-old/F	Spontaneous rupture of membranes, cervical insufficiency, preterm birth	Placenta/2x1 mm	The primordial adrenocortical cells may enter venous vessels during migration. Thus, they might reach the blood vessels within a stem villus of the placenta via shortcut vessels and the umbilical arteries.

Table 3. Continued

Reference	Age/gender	Presenting complaint	Location/size	Suggested pathogenesis
Kepes et al. (47), 1990	8 year-old/F	Bilateral leg pain	Spinal canal at the L2 level extramedullary/2.5*1.4*1.3 cm	Cells may have gained access to the spinal canal, perhaps following the sheath of an exiting nerve or the adventitia of an in-growing segmental lumbar artery of the aorta
Mitchell et al. (65), 1993	16 year-old/F	Intermittent pain in the thigh	Spinal canal at the L1-L2 level extramedullary/1.8*1.5*1.5 cm	N/A
	63 year-old/F	Burning and aching lower back pain	Spinal canal at the L4-L5 level extramedullary/1.5 cm	
Cassarino et al. (66), 2004	27 year-old/M	Lumbar pain, gait dysfunction, impotence, sphincter dysfunction	Spinal canal, intramedullary/3*2*1.8 cm	N/A
Karikari et al. (67), 2006	27 year-old/F	Bilateral leg pain, pollacuria	Spinal canal at the L2 level, intramedullary/3.6x2.3x1.1 cm	N/A (But supporting Kepes)
Schittenhelm et al. (68), 2008	44 year-old/F	Bilateral leg pain	Spinal canal at the L1 level, extramedullary/2.5 cm	N/A
Rodriguez et al. (69), 2009	5-month-old/F	Weakness in lower extremities	Spinal canal at the T10-L2, extramedullary/6x1.5 cm	N/A
Makino et al. (70), 2010	17-month-old/F	Inability to crawl and stand	Spinal canal at the T12-L1, L3-L4 extramedullary	N/A

USG: ultrasonography, CT: computed tomography, M: male, F: female, HBV: hepatitis B virus, HCV: hepatitis C virus, N/A: not available, N/D: not determined

particular importance in testicular involvement in children with congenital adrenal hyperplasia. Even if the testicular adrenal rest tumors are benign, they become hyperplastic and hypertrophic under the stimulation of ACTH. Due to their location in the rete testis, they consequently cause an obstruction of the seminiferous tubules with possible azoospermia and infertility. These tissues have also been demonstrated to secrete adrenocortical hormones, as shown by elevated hormone levels measured from the vein of the tumor compared to the peripheral blood. As already mentioned, there have been a few cases presenting with signs of virilization and Cushingoid appearance, presumably due to the increased levels of these hormones. Briefly, even if adrenal rest tumors are benign, they may become symptomatic due to either their hormonal function, mass effect, or both (17,20).

Conclusion

Ectopic adrenocortical tissue is not a rare entity, even in the healthy population. However, the mechanism of its emergence is not clearly understood and may differ from location to location, although several mechanisms have been proposed. A migration defect alone could be considered but is unlikely in cases when the ectopic adrenal tissues is distant from the original location. ACTH, with its endocrine or paracrine effect, SF-1 with its effect on stem cells or other as yet unknown factor(s) may also play a role. Further research is required on the subject of how adrenal tissues emerge in all these ectopic locations, given their important clinical consequences.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Oya Ercan, Design: Gürkan Tarçın, Oya Ercan, Data Collection or Processing: Gürkan Tarçın, Analysis or Interpretation: Gürkan Tarçın, Oya Ercan, Literature Search: Gürkan Tarçın, Writing: Gürkan Tarçın, Oya Ercan.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther 2019;10:68.

2. Basson MA. Signaling in cell differentiation and morphogenesis. Cold Spring Harb Perspect Biol 2012;4:a008151.

3. Kurosaka S, Kashina A. Cell biology of embryonic migration. Birth Defects Res C Embryo Today 2008;84:102-122.

4. Ozolek JA, Tekkesin MS. THE "-OMAS" and "-OPIAS": Targeted and Philosophical Considerations Regarding Hamartomas, Choristomas, Teratomas, Ectopias, and Heterotopias in Pediatric Otorhinolaryngologic Pathology. Head Neck Pathol 2021;15:25-40. Epub 2021 Mar 15

5. Barwick TD, Malhotra A, Webb JAW, Savage MO, Reznek RH. Embryology of the adrenal glands and its relevance to diagnostic imaging. Clin Radiol 2005;60:953-959.

6. Schechter DC. Aberrant adrenal tissue. Ann Surg 1968;167:421-426.

7. Marchand. Ueber accessorische Nebennieren im Ligamentum latum. Arch für Pathol Anat und Physiol und für Klin Med 1883;92:11-19.

8. Xing Y, Lerario AM, Rainey W, Hammer GD. Development of adrenal cortex zonation. Endocrinol Metab Clin North Am 2015;44:243-274.

9. Kim JH, Choi MH. Embryonic Development and Adult Regeneration of the Adrenal Gland. Endocrinol Metab (Seoul) 2020;35:765-773.

10. Yates R, Katugampola H, Cavlan D, Cogger K, Meimaridou E, Hughes C, Metherell L, Guasti L, King P. Adrenocortical development, maintenance, and disease. Curr Top Dev Biol 2013;106:239-312.

11. Claahsen-van der Grinten HL, Hermus AR, Otten BJ. Testicular adrenal rest tumours in congenital adrenal hyperplasia. Int J Pediatr Endocrinol 2009:624823. Epub 2009 Feb 26

12. Takahashi Y, Sipp D, Enomoto H. Tissue interactions in neural crest cell development and disease. Science 2013;341:860-863.

13. Furlan A, Dyachuk V, Kastriti ME, Calvo-Enrique L, Abdo H, Hadjab S, Chontorotzea T, Akkuratova N, Usoskin D, Kamenev D, Petersen J, Sunadome K, Memic F, Marklund U, Fried K, Topilko P, Lallemend F, Kharchenko PV, Ernfors P, Adameyko I. Multipotent peripheral glial cells generate neuroendocrine cells of the adrenal medulla. Science 2017;357:eaal3753.

14. Kastriti ME, Kameneva P, Adameyko I. Stem cells, evolutionary aspects and pathology of the adrenal medulla: A new developmental paradigm. Mol Cell Endocrinol 2020;518:110998. Epub 2020 Aug 18

15. Bholah R, Bunchman TE. Review of Pediatric Pheochromocytoma and Paraganglioma. Front Pediatr 2017;5:155.

16. Ohsugi H, Takizawa N, Kinoshita H, Matsuda T. Pheochromocytoma arising from an ectopic adrenal tissue in multiple endocrine neoplasia type 2A. Endocrinol Diabetes Metab Case Rep 2019;2019:19-0073.

17. Claahsen-van der Grinten HL, Sweep FC, Blickman JG, Hermus AR, Otten BJ. Prevalence of testicular adrenal rest tumours in male children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Eur J Endocrinol 2007;157:339-344.

18. Savaş C, Candir O, Bezir M, Cakmak M. Ectopic adrenocortical nodules along the spermatic cord of children. Int Urol Nephrol 2001;32:681-685.

19. El-maouche D, Arlt W, Merke DP. Congenital adrenal hyperplasia. Lancet 2017;390:2194-2210.

20. Engels M, Span PN, van Herwaarden AE, Sweep FCGJ, Stikkelbroeck NMML, Claahsen-van der Grinten HL. Testicular Adrenal Rest Tumors: Current Insights on Prevalence, Characteristics, Origin, and Treatment. Endocr Rev 2019;40:973-987.

21. Chang SP, Morrison HD, Nilsson F, Kenyon CJ, West JD, Morley SD. Cell proliferation, movement and differentiation during maintenance of the adult mouse adrenal cortex. PLoS One 2013;8:e81865.

22. Smeets EE, Span PN, van Herwaarden AE, Wevers RA, Hermus AR, Sweep FC, Claahsen-van der Grinten HL. Molecular characterization of testicular adrenal rest tumors in congenital adrenal hyperplasia: lesions with both adrenocortical and Leydig cell features. J Clin Endocrinol Metab 2015;100:524-530. Epub 2014 Dec 8

23. Claahsen-van der Grinten HL, Otten BJ, Sweep FC, Span PN, Ross HA, Meuleman EJ, Hermus AR. Testicular tumors in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency show functional features of adrenocortical tissue. J Clin Endocrinol Metab 2007;92:3674-3680. Epub 2007 Jun 26

24. Puar T, Engels M, van Herwaarden AE, Sweep FC, Hulsbergen-van de Kaa C, Kamphuis-van Ulzen K, Chortis V, Arlt W, Stikkelbroeck N, Claahsen-van der Grinten HL, Hermus AR. Bilateral Testicular Tumors Resulting in Recurrent Cushing Disease After Bilateral Adrenalectomy. J Clin Endocrinol Metab 2017;102:339-344.

25. Sullivan JG, Gohel M, Kinder RB. Ectopic adrenocortical tissue found at groin exploration in children: incidence in relation to diagnosis, age and sex. BJU Int 2005;95:407-410.

26. Chew KT, Abu MA, Arifuddin Y, Mohamed Ismail NA, Nasir NAM, Mohammed F, Nur Azurah AG. Ectopic adrenal tissue associated with borderline mucinous cystadenoma of ovary: a case report with review of the literature. Horm Mol Biol Clin Investig 2017;32.

27. Tingi E, Ogah J. Ectopic adrenal rest cells of the fallopian tube: a case report and review of the literature. J Obstet Gynaecol 2018;38:578-579. Epub 2018 Jan 31

28. Tong A, Jia A, Yan S, Zhang Y, Xie Y, Liu G. Ectopic cortisol-producing adrenocortical adenoma in the renal hilum: histopathological features and steroidogenic enzyme profile. Int J Clin Exp Pathol 2014;7:4415-4421.

29. Liu Y, Jiang Y-F, Wang Y-L, Cao H-Y, Wang L, Xu HT, Li QC, Qiu XS, Wang E Liu Y, Jiang YF, Wang YL, Cao HY, Wang L, Xu HT, Li QC, Qiu XS, Wang EH. Ectopic adrenocortical adenoma in the renal hilum: a case report and literature review. Diagn Pathol 2016;11:40.

30. Ferraz-de-Souza B, Lin L, Achermann JC. Steroidogenic factor-1 (SF-1, NR5A1) and human disease. Mol Cell Endocrinol 2011;336:198-205. Epub 2010 Nov 13

31. Ozisik G, Achermann JC, Meeks JJ, Jameson JL. SF1 in the Development of the Adrenal Gland and Gonads. Horm Res 2003;59:94-98.

32. Zubair M, Ishihara S, Oka S, Okumura K, Morohashi K. Two-step regulation of Ad4BP/SF-1 gene transcription during fetal adrenal development: initiation by a Hox-Pbx1-Prep1 complex and maintenance via autoregulation by Ad4BP/SF-1. Mol Cell Biol 2006;26:4111-4121.

33. Zubair M, Oka S, Parker KL, Morohashi K. Transgenic expression of Ad4BP/SF-1 in fetal adrenal progenitor cells leads to ectopic adrenal formation. Mol Endocrinol 2009;23:1657-1667. Epub 2009 Jul 23

34. Oka H, Kameya T, Sasano H, Aiba M, Kovacs K, Horvath E, Yokota Y, Kawano N, Yada K. Pituitary choristoma composed of corticotrophs and adrenocortical cells in the sella turcica. Virchows Arch 1996;427:613-617.

35. Turan H, Tarçın G, Mete Ö, Sinoplu AB, Evliyaoğlu SO, Öz B, Ercan O. Silent corticotroph tumor with adrenocortical choristoma in an eleven-year-old boy. J Clin Res Pediatr Endocrinol 2022;14:126-130. Epub 2021 Feb 15

36. Mete O, Ng T, Christie-David D, McMaster J, Asa SL. Silent corticotroph adenoma with adrenal cortical choristoma: a rare but distinct morphological entity. Endocr Pathol 2013;24:162-166.

37. Albuquerque FC, Weiss MH, Kovacs K, Horvath E, Sasano H, Hinton DR. A functioning composite "corticotroph" pituitary adenoma with interspersed adrenocortical cells. Pituitary 1999;1:279-284.

38. Coiré CI, Horvath E, Kovacs K, Smyth HS, Sasano H, Iino K, Feig DS. A composite silent corticotroph pituitary adenoma with interspersed adrenocortical cells: case report. Neurosurgery 1998;42:650-654.

39. Weltzien FA, Hildahl J, Hodne K, Okubo K, Haug TM. Embryonic development of gonadotrope cells and gonadotropic hormones--lessons from model fish. Mol Cell Endocrinol 2014;385:18-27. Epub 2013 Oct 18

40. Lotfi CFP, Kremer JL, Dos Santos Passaia B, Cavalcante IP. The human adrenal cortex: growth control and disorders. Clinics (Sao Paulo) 2018;73(Suppl 1):473.

41. Shigematsu K, Toriyama K, Kawai K, Takahara O. Ectopic adrenal tissue in the thorax : A case report with in situ hybridization and immunohistochemical studies. Pathol Res Pract 2007;203:543-548. Epub 2007 Jun 27

42. Medeiros LJ, Anasti J, Gardner KL, Pass HI, Nieman LK. Virilizing adrenal cortical neoplasm arising ectopically in the thorax. J Clin Endocrinol Metab 1992;75:1522-1525.

43. Wallace EZ, Leonidas JR, Stanek AE, Avramides A. Endocrine Studies in a Patient with Functioning Adrenal Rest Tumor of the Liver. Am J Med 1981;70:1122-1125.

44. Contreras P, Altieri E, Liberman C, Gac A, Rojas A, Ibarra A, Ravanal M, Serón-Ferré M. Adrenal rest tumor of the liver causing Cushing's syndrome: treatment with ketoconazole preceding an apparent surgical cure. J Clin Endocrinol Metab 2015;60:21-28.

45. Cox JN, Chavrier F. Heterotopic adrenocortical tissue within a placenta. Placenta 1980;1:131-133.

46. Sugiyama T, Tajiri T, Hiraiwa S, Inomoto C, Kajiwara H, Kojima S, Tobita K, Nakamura N. Hepatic adrenal rest tumor : Diagnostic pitfall and proposed algorithms to prevent misdiagnosis as lipid-rich hepatocellular carcinoma. Pathol Int 2015;65:95-99. Epub 2015 Jan 9

47. Kepes JJ, O'Boynick P, Jones S, Baum D, McMillan J, Adams ME. Adrenal cortical adenoma in the spinal canal of an 8-year-old girl. Am J Surg Pathol 1990;14:481-484.

48. Hamwi GJ, Gwinup G, Mostow JH, Besch PK. Activation of Testicular Adrenal Rest Tissue by Prolonged Excessive ACTH Production. J Clin Endocrinol Metab 1963;23:861-869.

49. Baranetsky NG, Zipser RD, Goebelsmann U, Kurman RJ, March CM, Morimoto I, Stanczyk FZ. Adrenocorticotropin-dependent virilizing paraovarian tumors in Nelson's syndrome. J Clin Endocrinol Metab 2015;49:381-386.

50. Johnson RE, Scheithauer B. Massive hyperplasia of testicular adrenal rests in a patient with Nelson's syndrome. Am J Clin Pathol 1982;77:501-507.

51. Verdonk C, Guerin C, Lufkin E, Hodgson SF. Activation of virilizing adrenal rest tissues by excessive ACTH production. An unusual presentation of Nelson's syndrome. Am J Med 1982;73:455-459.

52. Ntalles K, Kostoglou-Athanassiou I, Georgiou E, Ikkos D. Paratesticular tumours in a patient with Nelson's syndrome. Horm Res 1996;45:291-294.

53. Bozic C. Ectopic fetal adrenal cortex in the lung of a newborn. Virchows Arch A Pathol Anat Histol 1974;363:371-374.

54. Armin A, Castelli M. Congenital adrenal tissue in the lung with adrenal cytomegaly. Case report and review of the literature. Am J Clin Pathol 1984;82:225-228.

55. Ren PT, Fu H, He XW. Ectopic adrenal cortical adenoma in the gastric wall: case report. World J Gastroenterol 2013;19:778-780.

56. Arai K, Muro H, Suzuki M, Oba N, Ito K, Sasano H. Adrenal rest tumor of the liver : A case report with immunohistochemical investigation of steroidogenesis. Pathol Int 2000;50:244-248.

57. Tajima T, Funakoshi A, Ikeda Y, Hachitanda Y, Yamaguchi M, Yokota M, Yabuuchi H, Satoh T, Koga M. Nonfunctioning Adrenal Rest Tumor of the Liver : Radiologic Appearance. J Comput Assist Tomogr 2001;25:98-101.

58. Baba Y, Beppu T, Imai K, Masuda T, Iyama KI, Sasano H, Baba H. A case of adrenal rest tumor of the liver: Radiological imaging and immunohistochemical study of steroidogenic enzymes. Hepatol Res 2008;38:1154-1158. Epub 2008 Jun 17

59. Shin YM. Hepatic adrenal rest tumor mimicking hepatocellular carcinoma. Korean J Hepatol 2010;16:338-341.

60. Soo KL, Azhar R, Ooi LL. Hepatic adrenal rest tumour (HART): a case report. Ann Acad Med Singap 2014;43:120-122.

61. Valle RD, Montali F, Manuguerra R, Bresciani P. Adrenal rest tumour of the liver. Dig Liver Dis 2014;46:758. Epub 2014 Apr 3

62. Enjoji M, Sanada K, Seki R, Ito T, Maeda M. Adrenal Rest Tumor of the Liver Preoperatively Diagnosed as Hepatocellular Carcinoma. Case Rep Surg 2017;2017:8231943. Epub 2017 Jun 19

63. Qureshi F, Jacques SM. Adrenocortical Heterotopia in the Placenta. Pediatr Pathol Lab Med 1995;15:51-56.

64. Guschmann M, Vogel M, Urban M. Adrenal Tissue in the Placenta : a Heterotopia Caused by Migration and Embolism? Placenta 2000;21:427-431.

65. Mitchell A, Scheithauer BW, Sasano H, Hubbard EW, Ebersold MJ. Symptomatic intradural adrenal adenoma of the spinal nerve root: report of two cases. Neurosurgery 1993;32:658-661.

66. Cassarino DS, Santi M, Arruda A, Patrocinio R, Tsokos M, Ghatak N, Quezado M. Spinal adrenal cortical adenoma with oncocytic features: report of the first intramedullary case and review of the literature. Int J Surg Pathol 2004;12:259-264.

67. Karikari IO, Uschold TD, Selznick LA, Carter JH, Cummings TJ, Friedman AH. Primary spinal intramedullary adrenal cortical adenoma associated with spinal dysraphism: case report. Neurosurgery 2006;59:E1144.

68. Schittenhelm J, Ebner FH, Harter P, Bornemann A. Symptomatic Intraspinal Oncocytic Adrenocortical Adenoma. Endocr Pathol 2009;20:73-77.

69. Rodriguez FJ, Scheithauer BW, Erickson LA, Jenkins RB, Giannini C. Ectopic Low-grade Adrenocortical Carcinoma Immunohistochemical and Molecular Cytogenetic Study of a Pediatric Case. Am J Surg Pathol 2009;33:142-148.

70. Makino K, Kojima R, Nakamura H, Morioka M, Iyama K, Shigematsu K, Kuratsu J. Ectopic adrenal cortical adenoma in the spinal region: case report and review of the literature. Brain Tumor Pathol 2010;27:121-125. Epub 2010 Nov 3