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Renal-adrenal fusion: A literature review starting from a unique case in an anxious achondroplasia patient

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ABSTRACT

A rare renal-adrenal pathology found in an anxious and achondroplastic patient. The aim is to explore renal-adrenal fusion and to find a link between achondroplasia, anxiety and this extremely rare diagnosis, which was associated with another rare finding, an ectopic adrenal gland. Emphasis was put on the patient's medical decision having devastating results. Only 18 medical literature reports were found up until 2023 regarding renal-adrenal fusion, a diagnosis which is made mostly incidentally, in imaging studies. The case-based analysis was focused on the patient's background concurrent pathologies–achondroplasia and anxiety disorder, with literature insights on the renal-adrenal fusion (identified as a 1.8 × 1.7 × 0.7 cm mass on the superior renal pole) with ectopic adrenal gland. The patient's evolution from the initial uncertain diagnosis to the rash and anxiety-induced surgical decision (against medical advice), to the final diagnosis revealed by pathology examination. The rarity of this pathology and the complexity of the patient's case have important implications in clinical practice.

Keywords: reno-adrenal fusion, achondroplasia, anxiety, FGFR3, multidisciplinary

INTRODUCTION

Psychiatric disorders such as anxiety and depression are highly prevalent among people all around the world, with various outcomes regarding therapy and long-term follow-up, primary mental health needs not being met [1]. The effects of uncertainty intolerance on (general) anxiety can have detrimental effects on patients' quality of life, especially being associated with health anxiety through yet undetermined mechanisms (possibly anxiety sensitivity) [2, 3].

Although choices are usually the end result of deliberate and conscious processes, people choosing the most advantageous option from the perspective of the availability of their own resources, it is not always a rational behavior [4]. Unfortunately, the process of making a decision is not always the end-result of rational thinking, but one which involves intuition and personal emotions and experiences. Anxious patients (even more so in those with post-traumatic stress) have reported elements such as intuition and less rationality when faced with a decision-making event [3, 4].

Unfortunately, anxiety disorders can affect and be affected by physical health issues (as is the case of the patient), patients having difficulties managing their daily life tasks and experiencing anxiety due to their baseline illness, or, vice-versa, patients suffering from symptoms related to the impacts of anxiety, such as nervous system hyperactivity, muscle tension, digestive system issues (pain, nausea, bowel movement changes), insomnia, weakness/fatigue, dyspnea, tachycardia, hyperhidrosis, tremor [5-7].

Achondroplasia (an autosomal dominant disease with serious physical health issues) is the most frequent cause of short stature/dwarfism and this specific term was first used in the 19th century. Although prenatal diagnosis is available nowadays, it is most frequently diagnosed in early infancy [8]. This condition arises from a gain-of-function mutation involving the fibroblast growth factor receptor 3 (FGFR3) gene, with detrimental effects on endochondral ossification, a thus impaired process [9]. While this condition is primarily characterized by obvious physical manifestations such as short limbs, macrocephaly, and midface hypoplasia, its psychosocial impacts are equally significant. Individuals with achondroplasia often have to deal with unique challenges, including chronic pain, social stigmatization, and limited physical mobility, all of which contribute to an increased risk of mental health disorders, particularly anxiety, but also depression [10].

Studies have highlighted a higher prevalence of anxiety among individuals with achondroplasia compared with the general population. For instance, the studies in [11, 12] reported that children with achondroplasia exhibited heightened levels of anxiety, often linked to body image concerns and bullying. Additionally, adults with achondroplasia frequently face workplace discrimination and environmental barriers, further exacerbating feelings of worry and stress [10, 13]. Such challenges necessitate a multidisciplinary approach to care, addressing not only the physical but also the psychological needs of patients.

Understanding the interplay between the physical and emotional aspects of achondroplasia is critical for improving quality of life. This introduction aims to explore the link between achondroplasia and anxiety, emphasizing the importance of early intervention and tailored psychological support. It is also a preface for a special case presentation involving a major health decision of an achondroplasia patient, fueled by a concurrent anxiety and depression disorder, with devastating results.

CASE DESCRIPTION

The case of interest involves a 68 years old Caucasian female patient from Eastern Europe, suffering from achondroplasia, who addressed the department of urology of the 'Sfantul Apostol Andrei' Emergency Clinical Hospital of Galati, Romania, at the end of July 2024, for the following presenting complaints: fatigue, increased urinary frequency, left lumbar pain and hematuria. On clinical examination, no significant signs were identified and no palpable masses or abdominal tenderness were found. The relevant medical history of the patient included the aforementioned achondroplasia, osteopenia, hypertension, chronic venous insufficiency, steatosis, irritable bowel syndrome and anxiety.

On admission, complete blood count, blood urea and creatinine, urine analysis and urine cytology values were all within normal limits, revealing only a slightly elevated blood glucose level (185.95 mg/dl, with normal levels ranging from 70-115 mg/dl) and an alanine aminotransferase level of 37.28 U/L (normal ranges of 0-34 U/L). Imaging studies were done and on computer-tomography (CT) examination a superior pole renal tumor was identified. A diagnosis of left renal tumor with uncertain and unpredictable progression was made.

The management plan was discussed with the patient and surgical approach was recommended. Against all medical advice, the patient refused the procedure of sparing nephrectomy and opted for a total nephrectomy (very likely driven by the anxiety disorder from which the patient suffered, concurrently).

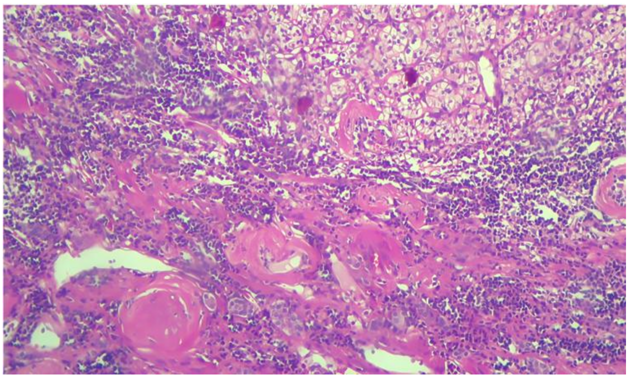

Figure 1. (200× HE) renal-adrenal fusion–Blending of the two separate parenchymas through inflammation, architectural distortion, with whisps of capsular clues (Source: Field study)

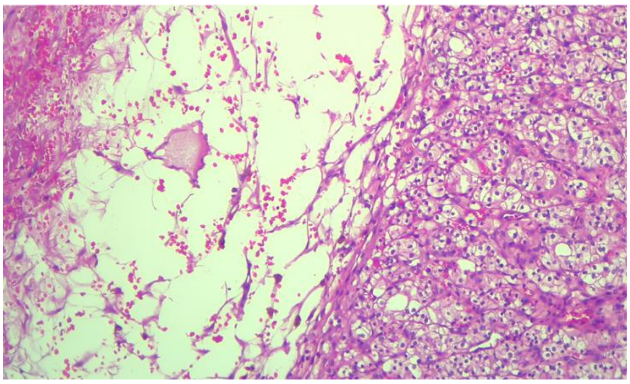

Figure 2. (200× HE) adrenal gland with cystic degeneration (Source: Field study)

The nephrectomy specimen was sent to the pathology laboratory for further workup. On gross examination the surgical piece measured a total of 17 × 8 × 6.5 [asaa1.1] [EN1.2] cm with an abundance of perirenal adipose tissue which revealed a very small flattened ovoid mass of 4 × 2 × 0.2 cm, yellow-orange, soft and pliable, with a heterogeneous aspect regarding the exterior and cut surface; the kidney itself measured 10.2 × 4.5 × 4 cm (with a 0.4 cm long ureter) and presented a cystic tumor mass located at the superior pole, apparently under the capsule (at 2.5 cm from the renal hilum), of 1.8/1.7/0.7 cm, on cut-surface being yellow-orange at the periphery with a reddish-brown, homogeneous center.

The histopathological examination revealed a complex diagnosis: the apical pole tumor was in fact identified as renal-adrenal fusion (**Figure 1**) with cystic degeneration of the adrenal parenchyma (**Figure 2**) (the surrounding renal parenchyma having changes of chronic inflammation, tubule thyroidisation and a background of benign nephronangiosclerosis–changes consistent with chronic pyelonephritis (**Figure 3**) and the apparent cause of renal-adrenal fusion in the patient's case), while the perirenal adipose tissue tumor was an ectopic/accessory adrenal gland with only cortical structure; focally, a capsular rest can be seen among the inflammatory and architectural changes.

Patient counselling was done with the recommendation of follow-up.

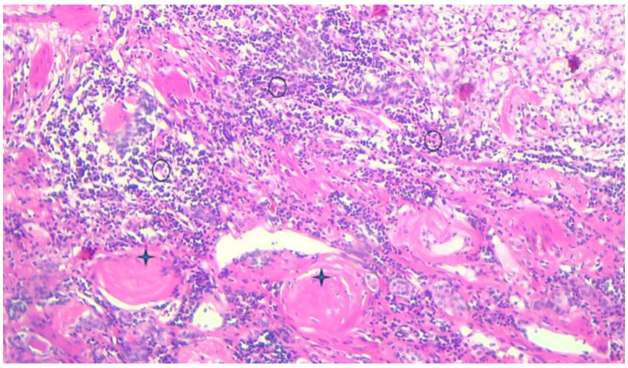

Figure 3. (200× HE) chronic pyelonephritic changes–Sclerosing glomeruli (stars) and chronic lymphocytic inflammation (circle); some tubule thyroidization (Source: Field study)

LITERATURE REVIEW AND DISCUSSION

Renal Adrenal Fusion and Achondroplasia–Rare Conditions-Diagnostic Challenges

Renal-adrenal fusion

First described in the medical literature by Rokitansky, in 1855 in his manual of pathological anatomy text, renal-adrenal fusion, a most frequently congenital anatomical anomaly, refers to the condition where the adrenal gland is fused to the kidney, typically affecting the upper pole of the kidney (complete or incomplete encapsulation/fusion during embryonic development–52 days post-conception due to retro-peritoneal mesenchymal cells' failure of stimulating the full development of the renal capsule); this rare anomaly of abnormally conjoined adrenal gland and kidney can also develop as a post-natal event, an acquired disorder, due to inflammation and subsequent fibrosis. Normally, the adrenal glands are located on top of the kidneys, but in renal-adrenal fusion, this anatomical relationship is disrupted [14-19]. The in-utero development (and differentiation) of the kidneys and adrenal glands is also heavily influenced by vasculogenesis and angiogenesis, a process based on the vascular endothelial growth factor (VEGF, also known as vascular permeability factor, but not exclusively), which could be evidenced immunohistochemically with the help of CD34 on specific tissues (and with the aid of differentiation and proliferation markers). This particular growth factor is involved in many kidney diseases, including polycystic kidney disease, acute renal allograft rejection, renal cell carcinoma, Wilm's tumor, and mostly solid tumors and metastasis, with influence on progranulin, an adipokine acting as another growth factor. VEGF could be a culprit in inflammatory angiogenesis which could lead to an eventual fusion through fibrosis, a process similarly found in fibrotic lung diseases where anti-VEGF treatment is recommended due to the aberrant inflammation and fibrosis of pulmonary parenchyma [20-27].

This rare condition is the beneficiary of only 18 medical literature reports up until 2023 [28]. It is often diagnosed incidentally during imaging studies (with frequent misdiagnosis due to the difficult nature of the mass–a mimicker so to speak, and un-necessary surgical intervention), but its clinical implications, particularly in patients with underlying genetic or syndromic conditions, warrant extensive evaluation. While some cases present as incidental findings during imaging for other reasons, as mentioned above, the underlying developmental anomalies may affect the renal and adrenal function [14-18, 29].

The diagnosis of renal-adrenal fusion is a difficult one–mostly found as an incidental mass, even though imaging studies have greatly evolved in the last century. The radiological aspects of this renal pathology are in fact the lack of a discrete fat plane between the superior kidney pole and the adrenal gland, with the presence (or not) of a continuous lesion/mass in the adjacent kidney. These particular aspects are difficult to interpret even on CT or magnetic resonance imaging (MRI) due to the motion artefacts given by the patient's respiratory function, making the diaphragm move. A positive indicator of a benign lesion favoring renal-adrenal lesion is the absence of a suspicious uptake on PET-CT examination. Thus being said, the current medical literature could benefit from extensive imaging studies of this particular pathology, being a limitation or gap in research [14].

Clinically and on imaging studies, renal-adrenal fusion can sometimes mimic other pathologies, including various tumors, cystic kidney disease, splenules and splenosis (ectopic spleen tissue as congenital lesions–splenunculi or accessory spleens, and, respectively acquired ones), exophytic gastric and hepatic lesions, celiac ganglion, periadrenal varix, adrenal pseudonodules, adrenal hyperplasia, simple adrenal cyst, cavernomas or metastases containing intracellular lipid, pheochromocytoma, adrenal carcinoma or adenoma (with or without lipomatous metaplasia), ganglioneuroma, adrenal myelolipoma or lymphoma, adrenal collision tumors, due to the similarities in their radiological appearance [30, 31]. Differentiating renal-adrenal fusion from these conditions is crucial, as management strategies can vary significantly based on the underlying diagnosis. Imaging studies such as ultrasound, CT scans, and MRI studies are critical tools in identifying renal-adrenal fusion, a pathology which is part of the "adrenal incidentalomas" group. On imaging, the fused organ will often appear as a single mass or structure, which can complicate diagnosis and lead to un-necessary interventions if not properly recognized [16, 18, 19, 29]. Regardless of the imaging studies, of the 18 cases of renal-adrenal fusion described in the medical literature, the gross pathological aspects were described as in **Table 1**.

Table 1. Gross aspects of renal-adrenal fusion [14-19, 29]

Lesions	Measurements	Gross description
Adrenal adenoma with renal-adrenal fusion [19]	11 × 7.2 × 6.8 cm	Golden-yellow mass, well-circumscribed, attached to the kidney
Adrenal adenoma with renal-adrenal fusion [18]	1.5 cm	Heterogeneous mass with circumscribed borders, adjacent to the kidney
Papillary renal cell carcinoma with renal adrenal fusion [17]	2 × 2 × 1 cm	-
Adrenal adenoma with renal-adrenal fusion [17]	'A small portion'	-
Adrenal adenoma with renal-adrenal fusion [15]	1.5 cm	-
Adrenal pseudocyst [14]	12 cm	Large cyst with grey-yellow wall, with compressed golden-yellow adrenal gland and yellow mucoid liquid
Bilateral renal-adrenal fusion, no associated lesions [13]	2.3 cm (each)	-

Table 2. Congenital anomalies associated with renal-adrenal fusion

Case	Congenital anomaly/anomalies
1	Meningomyelocele, ventriculomegaly, club feet, bilateral simian creases, partial agenesis of frontal bones
2	Arnold-Chiari malformation with ventriculomegaly, bilateral renal agenesis, a right testis located at the level of the adrenal, gastrointestinal tract malrotation, Meckel's diverticulum, and two smaller ileal diverticula
3	Bilateral renal agenesis, absence of the left diaphragmatic leaf, abnormally elongated ovaries, and a single accessory spleen
4	Arnold-Chiari malformation with marked hydrocephalus and polygyria, lumbosacral meningomyelocele, atretic left uterine cornu and fallopian tube, mispositioned left ovary, lumbosacral skin tag, and kyphoscoliosis with hypoplastic first, second, and third ribs on the left
5	Complete craniorachischisis with retroflexed neck consistent with iniencephaly, lateral facial clefts, cleft tongue, prominent midline bony excrescence of hard palate, laryngeal cleft, atrioventricular communis type of ventricular septal defect, single umbilical artery, small bowel malrotation, persistent omphalomesenteric duct, colonic atresia with absent anus, persistent vitelline artery, and sirenomelia with a single pelvic bone and two end-to-end long bones in a tapered lower extremity without a foot; agenesis of spleen, gallbladder, kidneys, ureters, bladder, urethra, uterus, and vagina, but ovaries were present
6	Bilateral trilobed lungs with epiarterial bronchi, situs inversus of spleen and accessory spleen, pancreas, stomach, and descending colon, a foreshortened mesenteric root, and a com plex cardiac malformation with pulmonic atresia, right aortic arch, absent right brachiocephalic trunk, anomalous origin of pulmonary arteries from separate ducti arteriosi (the right arising from the distal aortic arch, the left, from a left brachiocephalic trunk), left ventricular hypoplasia, and total anomalous pulmonary venous return to innominate vein

Table 3. Immunohistochemical expression of FGFR3 in normal tissues, with degree of intensity

Organ	Tissue segment	Intensity
Skin	Tunica media–dermal vessels, microvessels	+++
Heart	Tunica media–coronary arteries and veins, microvessels	+++
Lung	Respiratory epithelium submucosal glands, lamina propria fibroblasts	++
	Muscularis, microvessels	+
Kidney	Tunica media–renal artery and vein	+
Sublingual gland	Epithelia, tunica media of arterioles and veins	+++
	Microvessels	++
Submandibular gland	Ducts	+
	Tunica media of arterioles and veins, microvessels	+++
Duodenum	Epithelia (tips of villi) muscularis mucosae	++
Pancreas	Islets of langerhans	+++
	Tunica media–arterioles, veins	+
Liver	Hepatocytes	+++
	Bile duct epithelium	++
	Tunica media–portal tract vessels	+
Thyroid	Tunica media–arterioles and veins	+
Parathyroid	Chief and oxyphil cells	++
Pituitary	Acidophils and basophils	+
	Tunica media–arterioles and veins	+++
Adrenal cortex	Steroidogenic cells, tunica media–arterioles and veins, microvessels	++
Thymus	Tunica media–arterioles and veins	
Lymph nodes	Tunica media–arterioles and veins, microvessels	++
Cervix	Epithelia of endocervix, stromal fibroblasts, tunica media–arterioles and veins, microvessels	+++
Uterus	Stromal fibroblasts myometrium	++
	Tunica media–arterioles and venules	+
Breast	Epithelia of ducts, tunica media–arterioles and veins	++
	Microvessels	+
Placenta	Fetal vessels, connective tissue fibroblasts of chorionic villi	+++
Oviduct	Epithelia, muscularis	+
Testis	Microvessels	++
Prostate	Stromal smooth muscle cells	+
	Microvessels	++
Cornea	Epithelia, endothelium, fibroblasts in substantia propria	+++
Sympathetic ganglia	Schwann cells, microvessels	+++

Although a very rare pathology, adrenal congenital anomalies encompass a wide number of aspects, renal-adrenal fusion being just one of them; a study done on a pediatric/perinatal population of 3,537 autopsies, found in 6 cases adrenal anomalies, all associated with other congenital anomalies–**Table 2**, some cases being extreme and all ending with intrauterine or perinatal death [32]. This case associated only an ectopic adrenal gland, but with achondroplasia.

Achondroplasia

Achondroplasia, a form of short-limbed dwarfism, is caused by a mutation in the FGFR3 gene (the fibroblast growth factor receptor multigene family which includes–FGFR1, FGFR2, FGFR3, and FGFR4); this one condition might intersect with renal-adrenal fusion, as FGFR3 is found in various organs and tissues in the human body, in the epithelia and mesenchyme (**Table 3**), having an important functional role in normal tissue homeostasis. Achondroplasia is associated with various physical challenges, including limited mobility, increased susceptibility to musculoskeletal issues, but also psychosocial burdens. In patients with achondroplasia, there is a heightened risk for mental health issues, particularly anxiety, due to societal stigmatization and the challenges associated with the condition [8-10, 30, 33, 34].

Introducing Anxiety in the Mix

The intersection of renal-adrenal fusion with achondroplasia and anxiety disorder, particularly in terms of diagnostic complexities, clinical challenges, and the psychological burden faced by affected individuals is a major patient burden to bear. Furthermore, it emphasizes the need for a multidisciplinary approach to care that takes into account both the physical and psychological dimensions of managing patients with these conditions.

Although all of the tumors and pseudo-tumors listed above (as differential diagnoses for renal-adrenal fusion) are "invisible" pathologies, individuals suffering from achondroplasia (either as a single illness or an associated one in the same patient) often face significant psychosocial challenges due to the physical nature of the changes in the body. The visible nature of the condition leads to social stigmatization and discrimination, which can severely affect self-esteem and contribute to the development of anxiety and other mental health conditions, individual with achondroplasia suffering from elevated levels of psychological distress [10, 35-37]. Research indicates that individuals with achondroplasia are at a higher risk for anxiety, depression, and low quality of life, often due to the challenges they face in everyday life, including societal prejudice and limitations in physical functioning; in particular, anxiety is frequently reported as a major concern for these individuals, leading to social isolation, difficulties with employment, and challenges in establishing interpersonal relationships. and this particular mental health issue can lead to wrong medical decisions, impacting one's life in a detrimental manner [10, 12, 13, 35-38].

In patients with achondroplasia, the presence of renal-adrenal fusion complicates the clinical picture, necessitating a nuanced approach to diagnosis and treatment. Renal anomalies are common in individuals with achondroplasia, and these can include conditions such as renal agenesis, hydronephrosis, or renal malrotation [39]. The addition of a fused renal-adrenal structure can increase the complexity of the case, as the anatomical fusion may obscure the normal identification of renal or adrenal pathology.

When considering the psychological burden of living with achondroplasia, the diagnosis of renal-adrenal fusion may further exacerbate anxiety. The presence of another potential health concern can contribute to heightened feelings of uncertainty and worries, particularly when the diagnosis is uncertain, or when the patient is subjected to invasive procedures for further investigation [36, 38, 40]. Patients with achondroplasia may have higher degrees of medical anxiety, particularly when faced with repeated medical evaluations or procedures due to the stress of managing a congenital physical condition, but with the added psychological toll of dealing with renal-adrenal fusion can create a cyclical pattern of exacerbated mental health symptoms, leading to poorer outcomes, most patients with achondroplasia having a diagnosed psychiatric disorder. Even more so, the quality of life of achondroplastic patients is generally lower than non-achondroplastic individuals, and this difference can be seen among male and female patients, females being generally more affected than males; these health status quality impairments can also have social and economic consequences (welfare) [40-42].

Multidisciplinary Management

Additionally, regarding the management plan for such a complex patient with 3 major comorbidities (renal-adrenal fusion, achondroplasia and anxiety), the individual's psychological well-being should be considered an integral part of the treatment plan making it essential to incorporate mental health support into the care plan. Cognitive behavioral therapy and other types of psychological intervention have been shown to improve coping strategies and reduce anxiety in individuals with chronic health conditions (such as chronic obstructive pulmonary disease, arthritis, epilepsy, irritable bowel syndrome, fatigue, tinnitus, brain injury, migraines, circulatory diseases, etc.) [43]. In addition to psychological counseling, patients with achondroplasia may benefit from social support programs that focus on enhancing social interactions and reducing isolation, which can further contribute to improved mental health out-comes [32, 44]. One must bear in mind the fact that the COVID-19 has had a major impact on the psychological wellbeing of the general population, and even more so on the susceptible population with physical and mental disabilities (as in this patient's case) [45-50].

The management of renal-adrenal fusion itself may not always require surgical intervention unless the fused organs are causing functional impairment or associated complications (such as is the patient's case, the cystic degeneration of the adrenal gland). If surgical intervention is required, careful consideration must be given to the patient's overall health, including any coexisting conditions such as spinal or foramen magnum stenosis or respiratory issues, hydrocephalus, which are common in patients with achondroplasia [51-52]. Furthermore, the surgical approach must take into account the potential difficulty of accessing the fused organs due to anatomical variations and the close proximity of the adrenal tissue to the renal parenchyma, surgical approach and resection margins representing a priority in any pathology [53].

Additionally, the physical aspects of renal-adrenal fusion, including the potential for renal or adrenal dysfunction, must be closely monitored. While renal-adrenal fusion itself may not always result in functional impairment, its association with other congenital urological (or other organ system) anomalies should prompt careful evaluation of renal and adrenal function; possible causes for such developmental issues would benefit from further research (certain food intakes could increase toxicity due to contaminants, in utero) [54], as would other associating diseases [55-57]. Major surgery in itself is a prime health risk [58], but regular follow-up imaging and laboratory tests to assess renal and adrenal function are crucial for preventing long-term complications in such patients.

Critical Appraisal

1. The complex pathology presented in the current paper is an extremely rare one, be it only renal-adrenal fusion (with only 18 cases presented in the worldwide medical literature), or in association with achondroplasia, ectopic adrenal gland and anxiety disorder. Renal-adrenal fusion is reported to be associated with other congenital anomalies in the medical literature [32].
2. The positive diagnosis of renal-adrenal fusion was made on histopathological examination, as clinically and in imaging studies this entity was not even considered in the differential diagnosis.

3. In an effort to characterize this entity with more accuracy and in order to avoid unnecessary surgical interventions, imaging studies' description was made and differential diagnoses were listed in order to have an exclusion list.
4. The medical literature lacks in renal-adrenal fusion studies, having a grey area in regards to its signs and symptoms, imaging studies characteristics and possible pre-surgical positive diagnosis alternatives–such as frozen section examination [18].
5. Nevertheless, this entity should always be on the physician's radar when dealing with a pathology located in the renal space. Radical nephrectomy is the preferred treatment choice in cases of a presumed malignant tumor of the kidney, as was the case of this patient, but not an only one; lesion-specific strategies is a future research direction, albeit on a very specific, targeted pathology [59, 60].

CONCLUSIONS

Renal-adrenal fusion (along with accessory adrenal gland) in patients with achondroplasia is a very rare entity and presents a unique set of challenges that extend beyond the physical aspects of the condition. The presence of this anomaly requires careful diagnostic workup in order to distinguish it from other pathologies and to determine the best course of action. Moreover, the psychosocial burden of living with achondroplasia, a congenital defect, associated with anxiety and other mental health issues, requires an extensive, multidisciplinary approach to patient care. Physicians must be aware of the heightened risk of anxiety in these patients and provide appropriate psychological support alongside physical treatment. Ultimately, managing renal-adrenal fusion in an anxious patient with achondroplasia needs a delicate balance between addressing the physical and emotional needs of the patient, with focus on the therapeutic approach in the setting of uncertain clinical and imaging diagnostic elements.

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