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EDITORIAL

# THE FUTURE OF BIOMEDICAL ENGINEERING AND MEDICINE IN THE ERA OF ARTIFICIAL INTELLIGENCE

Sezer Ulukaya

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With the increasing computational capacity and the artificial intelligence revolution, solutions to many complex problems have begun to be sought from an interdisciplinary perspective in medical and biomedical engineering in recent years. Thanks to the ability of artificial intelligence to analyze large amounts of multi-dimensional data faster than humans, it has become possible to both save time and reveal deep relationships that cannot be seen with the naked eye. Producing medical solutions in the biomedical field using artificial intelligence tools that are developing at a dizzying pace will save doctors time, increase digitalization in healthcare, and provide doctors with concise and in-depth analysis information by analyzing big health data with computerized decision support systems. The opportunities offered by artificial intelligence in the field of medicine seem to be the scene of groundbreaking developments. In the field of preventive cardiology, voice and retinal fundus data analysis for cardiovascular risk stratification may be new biomarker candidates (1). Based on the responses of the large language model to the commands created by the researcher, artificial intelligence will be able to analyze patient history and anamnesis in the fields of radiology, pathology, surgery, and oncology, and create a personalized care plan in the field of precision medicine (2). According to the international guideline proposed by a multidisciplinary team, in addition to the opportunities offered by artificial intelligence, risks such as protecting data privacy, explaining the model, determining responsibility in case of erroneous decisions, and biased attitudes come to the fore (3). Successful results have been obtained in predicting the survival time of cancer patients using artificial intelligence based on facial images, and it has been evaluated that it may be used in personalized treatment planning (4). As a result of the pioneering impact of artificial intelligence on drug design, a new class of antibiotics effective against resistant bacteria has been discovered (5). With digital twins, surgical procedures can be simulated and personalized treatment processes can be optimized through virtual copies of individuals (6). Although artificial intelligence has disadvantages such as the need for a lot of data, biased attitude, explainability, and privacy, it will be able to solve many complex problems by contributing to the multidisciplinary perspective in biomedical and medical fields, save time for physicians, and contribute to resource savings by planning personalized treatments for patients.

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REVIEW

# ÜNER TAN SYNDROME: A REVIEW OF THE SYNDROME AND REVERSE EVOLUTION

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## ABSTRACT

Üner Tan syndrome is a rare genetic condition that primarily affects individuals from consanguineous families, marked by a distinct quadrupedal gait, intellectual disability, and limited speech. First identified in Türkiye in 2005, Üner Tan syndrome has since been recognized in various regions with similar patterns of consanguinity. Those with Üner Tan syndrome commonly exhibit a diagonal-sequence quadrupedal gait, which led Üner Tan to propose the theory of "reverse evolution," suggesting that affected individuals represent a regression to a more primitive state, losing advanced human traits such as upright walking, speech, and cognitive abilities. This theory has sparked significant debate in both medical and evolutionary circles. Neurological and genetic studies have pointed to certain mutations that play a role in the syndrome, with cerebellar hypoplasia frequently detected in brain scans. The disorder sets itself apart from other conditions like cerebral palsy and congenital ataxias due to the absence of congenital hypotonia and the preservation of muscle strength. However, affected individuals often struggle with bipedal movement, instead relying on quadrupedalism as their primary means of locomotion. This phenomenon is linked to the dysfunction of central pattern generators, neural networks that typically coordinate rhythmic movements like walking. In Üner Tan syndrome patients, these central pattern generators appear impaired, leading to a preferance for quadrupedalism over bipedalism.

Despite the severity of intellectual impairment, the exact cause of the cognitive dysfunction in Üner Tan syndrome remains elusive, though it is thought to involve a combination of genetic mutations affecting brain development. In addition to cerebellar atrophy, imaging often shows mild cerebral atrophy. The rarity of Üner Tan syndrome, its overlap with other conditions, and the absence of clear diagnostic criteria make it challenging to diagnose, further complicating clinical understanding of the syndrome. The concept of reverse evolution in Üner Tan syndrome has also led to interesting discussions in evolutionary biology. There is a controversial notion that challenges traditional ideas about evolution by suggesting that mutations can cause the loss of higher-order human traits and revert individuals to a more ancestral form. This idea parallels some observations in other biological processes, such as the metabolic shifts seen in cancer cells, where cells revert to more primitive states to survive. However, it's important to take this notion into consideration with caution since it is still a subject of debate. In conclusion, Üner Tan syndrome is a complex condition that offers valuable insights into human development, genetics, and the potential for reverse evolutionary processes. Further research is needed to clarify its genetic underpinnings and its implications for understanding human evolution and disease.

**Keywords:** Ataxia, consanguinity, hypotonia, intellectual disability

## INTRODUCTION

Üner Tan syndrome (UTS) is a syndrome characterized by diagonal-sequence quadrupedal gait, intellectual disability, and rudimentary speech (1). Üner Tan first discovered a family that had members thought to have UTS symptoms in İskenderun, a region in Hatay, Türkiye in 2005. In 2006, new families with members that had the same symptoms were discovered in the cities, of Adana and Gaziantep. Later on, cases in cities such as Çanakkale and İstanbul proved that the syndrome was not a special condition within a specific geographic region, as they weren't in Southern Türkiye like the previous cases (1). The Anatolian region has a long history of quadrupedalism; in fact, the first person to use their four limbs and have UTS symptoms was discovered in the Havza region of Samsun. This person was photographed by a British photographer, W. J. Childs, in 1917. This man was thought to belong to a consanguineous Greek family as Greek people tended to live in that region during the Ottoman Empire's reign in isolation and practiced

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incestual relationships (2). UTS is an autosomal recessive disease, it is almost exclusively seen in consanguineous families and is seen in closed populations that practice intrafamilial marriages (3). Üner Tan himself described the syndrome as a "backward (reverse) evolution" (4). This sparked controversy among evolutionary scientists and medical authorities as the irreversibility of evolution has been a staple theme for a long time (5).

**Experimental Reverse Evolution and Reverse Evolution in Nature**

Reverse evolution is explained as the reacquisition of at least one of the ancestral traits by derived populations, thereby resembling ancestor populations to a certain degree (5). In the laboratory, the possibility of reverse evolution can be easily examined by creating mutants resistant to antibiotics and allowing them to develop in environments deprived of antibiotics. Although phenotypic reversion of antibiotic resistance has been documented, evolutionary reversions involving the spread of antibiotic- sensitive wild-type alleles are quite rare in nature and only take place in highly selective environments with high mutation rates such as laboratory studies that introduce specific alleles in antibiotic-free environments (6).

When discussing reverse evolution, two different types of genetic mechanisms need to be recognized: those that aid the process of reversal and those that totally prevent or partially prevent the process of reversal. Generally, pleiotropy and random mutations aid in reverse evolution (5). Total reverse evolution in multicellular organisms is particularly difficult because of epistasis, the interaction between genes at different loci, where the expression of one gene depends on the presence of alleles at another gene locus (5, 7).

Attempts to reversely evolve viruses and bacteria have been made in the past with few of them succeeding, reverting the organism close to the ancestral levels (5). It has been demonstrated in some studies that evolution in reverse is possible in both short-term, experimentally controlled studies of populations and over long evolutionary histories encompassing the diversification of large groups of species. These studies have focused on opposite extremes of the reversibility spectrum with respect to time span (8). A study made on *Plasmodium vivax* to understand the mechanism of microbial resistance has found that a particular single-point mutation, the amino acid at position 117 that is changed from serine to asparagine (S117N), serves as a turning point in the evolution of high resistance regions by generating epistatic interactions that obstruct the reverse evolution of the gene back toward the wild-type ancestor which doesn't have antimicrobial resistance (9). An experiment used an ancestral form of *Pseudomonas fluorescens* in an attempt to investigate evolutionary diversification when faced with geographical heterogeneity. Asexually reproduced bacteria in a different culture than their ancestors' developed a wrinkly fuzzy form in 7 days, differing from their smooth ancestors. However, when these "evolved" bacteria were put into their ancestor's culture, and then these bacteria "reverted" their ancestral smooth form which was more suitable for the culture.

This suggests that the wrinkled phenotype was not a fixed product of evolution (10). In another study, the researchers worked with *Helicobacter pylori (H. pylori). H. pylori* is a bacterial species that includes strains resistant to antibiotics such as Kanamycin and Clarithromycin. The researchers explored horizontal gene transfer, finding that higher transformation rates can spread non-resistant alleles and partially reverse antibiotic resistance in some populations (6).

Some laboratory experiments have been conducted on sexually reproducing multicellular organisms as well to determine whether reverse evolution in a highly selective environment is possible (11). In an experiment conducted in 2002 on *Drosophila* (fruit flies), these flies shared a common ancestry but were raised under different selective pressures, such as late-life fertility, starvation resistance, and accelerated development. The animals were then placed in the same ancestral environment and bred for 50 generations. The experiment concluded that some aspects of male fitness reverted to their ancestral levels such as survival time, offspring's viability, and mating success; female flies didn't show such strong evidence of reverse evolution of fitness. Although the fitness of female flies didn't show significant change, some groups of the population had limited differentiation observed in fecundity characteristics but this differentiation wasn't widespread as well (11, 12). The outcome might be explained by theories like differences between the inheritance of male and female traits and/or having different environmental sensitivity levels than males (11).

In another study, the reversal of adaptation to the ancestral state by back amino acid replacement has also been documented. *Rhodopsin1 (RH1)* gene sequences that encode rhodopsin, a protein that makes it possible to form images in light-deficient environments, from cichlid fishes across four tribes in Lake Tanganyika, each inhabiting different depth habitats, have been studied. The species generally exhibited two RH1 variants: 292A for shallow-water species and 292S for deep-water species, tailored to their respective light environments as confirmed by pigment absorption spectra.

Findings reveal two distinct patterns of parallel adaptive evolution to the depth of water: the A292S substitution occurred independently at least four times, facilitating adaptation from shallow to deep water environments. Conversely, the reverse substitution S292A occurred three times, enabling adaptation from deep to shallow water habitats. This dual adaptation demonstrates a complete reverse evolution scenario where adaptive mutations in RH1 pigments coincide with shifts in species' habitats, marking a notable example of genetic adaptation to environmental changes (13).

**Cancer and Reverse Evolution**

Cancer is greatly connected to many biomechanisms, one of them being reverse evolution. The study of evolutionary reversibility in enzymes has shown how genetic pathways can

shift in response to environmental pressures, a principle that can also apply to multicellular organisms where cells may "reverse" to a more primitive, survival-driven state (14). Cancer is caused by various factors, including genetic mutations, viral, bacterial, fungal, and parasitic infections, environmental agents like toxins and radiation, and lifestyle factors such as smoking, alcohol, poor diet, obesity, and inactivity (15).

Interestingly, similar to the adaptive gene network reversals observed in yeasts, which switch their metabolism to enhance survival under stress, cancer cells also undergo metabolic reprogramming, allowing them to more efficiently utilize energy for rapid growth and survival (16). The idea that cancer develops by disturbing the genetic network underlying multicellularity is supported by the discovery of an increased percentage of cancer promoters on branches linked to the formation of metazoan multicellularity (17).

Cancer cells use glycolysis to provide energy to the cell even in the presence of oxygen, this is less effective than oxidative phosphorylation. This phenomenon is known as the "Warburg effect" (18). Warburg effect is thought to occur for different reasons, one of them being the fast and uncontrolled proliferation of cancer cells; glycolysis is faster than oxidative phosphorylation, thus allowing faster growth (19). In addition, cancer cells usually overgrow their blood supply, meaning that the oxygenation of cells will not be sufficient after some point, and oxygen will be scarce. Using glycogen for adenosine triphosphate (ATP) production resolves this issue (20). Increased lactate will acidify the cell eventually and this will promote metastasis while also suppressing immune response (20, 21). Switching to the Warburg effect, meaning the preference for glycogen instead of oxygen is a sign of cells acquiring a more primitive state in terms of metabolism (18). Mitochondria being rendered useless because of the preference for glycogen has some scientists claim that cells undergo "de-endosymbiosis", further claiming this shift in cancer cells proves reverse evolution in cancer cells (18).

**UTS and Human (De-)Evolution**

UTS patients are usually unable to move bipedally and usually they have never exhibited such behavior (22). The development of extensor motor system dominance over the flexor motor system during sitting, standing, and walking led to the emergence of bipedalism. The dominance of the extensor motor system over the flexor motor system is attributed to the skeletal muscles, which are responsible for maintaining upright posture by acting against gravity alongside a healthy nervous system (23).

There are various hypotheses exploring the purpose and advantages of bipedalism of humans. The emergence of bipedalism dates back to around 7 million years ago. This shift from quadrupedalism likely involved a gradual transition from more compliant, ape-like gaits to the stiffer, more efficient bipedalism seen in modern humans, driven by anatomical adaptations that facilitated upright posture and movement, a process that may have been influenced by environmental and functional factors (24). People with UTS generally use quadrupedalism as a way of locomotion with skill and ease. Some patients may use quadrupedalism habitually, switching between bipedalism and quadrupedalism while some never gain the ability to ambulance bipedally (25). Üner Tan used the term "evolution in reverse" for UTS because it seemed as if this "mysterious condition" took away all the great gifts of evolution: speech, bipedal locomotion, and intelligence (26).

Intelligence is almost always impaired severely with very few exceptions and speech is always rudimentary if not absent (25). Üner Tan has postulated that quadrupedalism in people with UTS happens in three stages.

The first phase, termed primary variability, occurs during fetal development and infancy, encompassing both typical and abnormal cases such as UTS. In this phase, the neural foundation for locomotion is established based on evolutionary epigenetic mechanisms inherited from primitive tetrapods that lived approximately 400 million years ago. Through self-generated motor activity and afferent information transmission within the neural system, the groundwork for quadrupedal locomotion is laid down, drawing upon ancient neural networks (27).

The second phase involves a neuronal selection process occurring during infancy. Here, the most effective motor patterns and associated neuronal groups are chosen based on experience. In normal cases, this phase leads to the selection of neural networks conducive to bipedal walking. However, in UTS cases, where certain neural structures necessary for upright walking are compromised due to conditions like cerebellar hypoplasia, the selection process diverges, favoring the enhancement of neuronal groups related to diagonal-sequence quadrupedal locomotion (27).

The third phase, termed secondary or adaptive variability, begins around two to three years of age and extends into adolescence. During this phase, secondary neural repertoires are developed through diverse motor experiences, allowing for the precise adaptation of movements to specific tasks. In individuals with UTS, this phase is hindered, leading to the retention of primitive motor repertoires from earlier phases and limiting the creation of secondary neural repertoires. Consequently, these individuals may continue to rely on ancestral neural groups associated with quadrupedal locomotion. The duration of this phase may vary, with some individuals experiencing delays in the emergence of well-balanced quadrupedal locomotion, which may only manifest late in adolescence (27).

As for the intelligence and dysarthric speech of people with UTS, several hypotheses have been proposed, but an exact cause has still not been found, as is the case with quadrupedalism. Intellectual disability seen in individuals with UTS is thought to stem from a combination of genetic, neurological, and developmental factors. Phenotypic changes that affect brain development and function, leading to structural abnormalities such as cerebellar atrophy and mild cerebral atrophy, are observed in magnetic resonance imaging examinations (28, 29).

Furthermore, neurological dysfunction, including severe intellectual disability and speech disturbance, is common in individuals with UTS. These cognitive impairments may result from disruptions in brain regions beyond the cerebellum, suggesting a multifaceted etiology that may include genetics, cerebral impairments, and environmental factors (22, 28).

Mental impairment, cerebellar hypoplasia, and varying walking gaits have been observed in UTS. These symptoms are obvious especially when it comes to gait as some patients habitually use quadrupedalism (30). Üner Tan proposed that central pattern generators (CPGs), a neural network system that is used to create rhythmic, coordinated movement, such as walking and running, may be the main etiological cause of UTS. One of the main theories in UTS is that quadrupedalism may be caused by malfunctioning CPG circuits. Cerebellar atrophy in these patients may result in loss of coordination and balance, making it difficult for them to walk normally on two feet and therefore making them favor quadrupedal gait. The CPG's function in movement implies that variations in UTS symptoms, such as the degree of quadrupedalism or motor impairment, could result from different spinal locomotor circuit dysfunctions (31). As an example of the various presentations of the syndrome, Üner Tan reports on some members of the Adana-1 family who are able to walk backward and forwards bipedally while still suffering from UTS (32).

On the other hand, UTS patients are frequently thought to represent a phenotypic diversity of cerebral palsy and many of them stay undiagnosed. Several congenital ataxias, including Cayman syndrome, Gillespie syndrome, Disequilibrium syndrome, and Joubert syndrome, have symptoms that overlap with UTS. The absence of congenital hypotonia, maintained muscle strength, early gait acquisition, and quadrupedal movement are important characteristics that set UTS apart. Furthermore, brain imaging of patients with UTS usually shows cerebellar hypoplasia (22).

The reverse evolution thought to take place in the UTS has been associated and explained with certain morphological, neural, and genetic factors. The brachial index, which has decreased throughout hominin evolution, in patients with UTS is more similar to that of Pan paniscus (bonobos), Australopithecus afarensis (A. afarensis, Lucy), Homo habilis, than Homo sapiens. Additionally, the body mass distribution in the footfall patterns of UTS patients reveals reduced support on their hands relative to their feet, a pattern consistent with observations in non-human primates. In accordance with the principles of Darwinian medicine, Özçelik et al. (32) also highlight morphological features such as the supraorbital torus. Furthermore, the genetic traits and functional characteristics associated with UTS have been proposed as indicators of reverse evolution, a concept that is further elaborated upon in the upcoming section (32).

### Genetic Factors in UTS

Variations of presentations due to various genetic mutations prove this syndrome rather unique (Table 1) (30). The genetic examinations of the 33 primary cases included in Üner Tan's original study indicate the heterogeneous genetic background of the syndrome (32). In the İskenderun family, the genetic mutation involved the WD repeat domain 81 (WDR81). In the Çanakkale and Antep families, the affected region on the chromosome included the very low-density lipoprotein receptor (32). Carbonic anhydrase 8 (CA8) was affected in the Iraqi family. In addition to these cases, a case with inositol 1,4,5-triphosphate receptor type 1 (ITPR1) mutation from Brazil with UTS has been reported (22).

WD repeat domain 81, VLDR, and CA8 are genes that have previously been associated with quadrupedal gait alongside ITPR1, tubulin beta 2B class IIb (TUBB2B), and ATP phospholipid transporting 8A2 (ATP8A2) (22). These individual genes are linked to the production of proteins crucial for the structural and functional organization of the brain, including the cerebellum, which governs locomotor coordination and trunk balance. It has been suggested that these mutations likely played a role in the development of quadrupedal locomotion in humans (32). Although this suggests a possible genetic background for UTS, many recorded cases lack a specific genetic diagnosis (22).

**Table 1. Genetic mutations that are observed to cause UTS**

| Genes | Affected functions |
|---|---|
| *ITPR1* | Mutations might disrupt calcium homeostasis, leading to impaired function and degeneration of Purkinje cells (23). |
| *TUBB2B* | Mutations in the *TUBB2B* gene, which is involved with β-tubulin production, might cause disruptions in microtubule stability, causing impairments in neuronal migration and axonal development (30). |
| *VLDLR* | Mutations in the *VLDLR* gene might disrupt the Reelin signaling pathway, resulting in abnormal neuronal migration and cerebellar hypoplasia (34). |
| *PIGG* | Disruptions in glycosylphosphatidylinositol (GPI), which is encoded by the *PIGG* gene, might cause deficiencies in GPI-anchored proteins, preventing other proteins' binding ability to the cell. This might impair neurons and their function (35). |
| *CA8* | Mutations in CA8 might disrupt ion homeostasis and intracellular signaling, leading to cerebellar ataxia and cerebellar atrophy (23). |
| *WDR81* | Mutations might impair endosomal and lysosomal functions, leading to neurodegenerative changes and cerebellar atrophy (23). |
| *ATP8A2* | ATP8A2 protein ensures the asymmetry of phospholipids in the plasma membrane. Missense mutations disrupt protein's function, leading to defects in cell membrane structure and signalling (23). |

ITPR1: Inositol 1,4,5-triphosphate receptor type 1, TUBB2B: Tubulin beta 2B class IIb, VLDLR: Very low-density lipoprotein receptor, PIGG: Phosphatidylinositol glycan anchor biosyhthesis, class G, CA8: Carbonic anhydrase 8, WDR81: WD repeat domain 81, ATP8A2: Adenosine triphosphatase phospholipid transporting 8A2, UTS: Üner Tan syndrome

Additionally, it has been suggested by Özçelik et al. (32) that maternal diabetes, type-1 diabetes in the case of the Iskenderun family, may add to the genetic defect via furthering prenatal neural damage.

## CONCLUSION

Diagnosing UTS is challenging due to its rarity and consequent lack of awareness, limited research, overlapping symptoms with other neurological and genetic disorders, variability in symptom severity and comorbid conditions, absence of standardized diagnostic criteria, reliance on subjective assessments, complex and not well-understood genetic basis, need for a multidisciplinary approach, and the necessity for comprehensive evaluations including detailed clinical history, neuroimaging, and advanced genetic testing. Especially in countries where consanguineous marriages are common, doctors should be educated on UTS, through family history and the ability to obtain one is crucial when diagnosing hereditary rare disorders.

The consequences of consanguineous marriages extend beyond UTS, leading to a higher prevalence of various genetic disorders, congenital malformations, and developmental delays. Addressing these issues requires public health interventions, including genetic counseling and education to inform at-risk populations about the potential risks associated with consanguineous marriages. Additionally, promoting genetic screening and providing resources for family planning can help mitigate the incidence of inherited disorders in populations where consanguineous marriages are culturally prevalent.

Moreover, when discussing reverse evolution, it is important to recognize the genetic mechanisms that aid the process of reversal, such as pleiotropy and random mutations, as well as the inhibitory effects of epistasis in multicellular organisms. Experimental evidence of reverse evolution, including studies on Plasmodium vivax and ancestral forms of bacteria, provides valuable insights into the dynamic and context-dependent nature of reverse evolution in microbial populations. These insights contribute to the ongoing discourse in the scientific community and underscore the need for further research on the genetic mechanisms underlying evolutionary reversions.

***Ethics***

***Informed Consent:*** *Not required.*

***Footnotes***

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CASE REPORT

# MODERN SURGICAL APPROACH IN VERTEBRA PLANA: BALLOON KYPHOPLASTY AS AN INNOVATIVE TREATMENT-A CASE REPORT

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## ABSTRACT

Vertebra plana is often asymptomatic and typically identified as a radiological finding. It is characterized by a 70% loss in vertebral height without kyphosis. In patients experiencing pain and functional loss, surgery is an option that should be considered. This case aims to share the clinical improvement findings after kyphoplasty surgery in a patient with vertebra plana. A 69-year-old female patient presented to the Department of Neurosurgery clinic due to low back pain while walking. Radiological imaging revealed a lumbar vertebrae 1 compression fracture with approximately 75% loss of vertebral height. The patient underwent balloon kyphoplasty. Vertebral height loss was successfully restored by an estimated 5-8 mm. No perioperative complications were reported. Vertebra plana is usually detected incidentally in asymptomatic patients. However, this case demonstrates that it can cause symptoms such as pain and that balloon kyphoplasty can be a viable treatment option in such situations

**Keywords:** Kyphoplasty, osteoporosis, spine

## INTRODUCTION

Vertebra plana is a radiological finding characterized by a reduction in vertebral body height exceeding 70%, frequently associated with osteoporotic compression fractures (1, 2). It is often identified incidentally in asymptomatic patients (3, 4). However, in certain cases, it may manifest acute or chronic pain, neurological deficits, or kyphotic deformity in the affected segment (4, 5).

Asymptomatic individuals are typically managed conservatively, without the need for surgical intervention. However, in patients presenting with significant symptoms, such as pain or functional impairment, surgery may be considered. Among these, vertebroplasty and kyphoplasty are prominent techniques frequently used in clinical practice (3, 5). These procedures are generally unsuitable for advanced vertebral collapse, such as vertebra plana, as restoring vertebral height poses significant challenges (6).

The primary objectives of surgical intervention are to prevent spinal deformity, restore vertebral body height, alleviate pain, and improve the patient's functional capacity, facilitating early mobilization and enhanced quality of life (3, 4).

This case report highlights the successful treatment of a patient with vertebra plana using kyphoplasty, demonstrating the efficacy of this approach in achieving favorable clinical outcomes.

## CASE REPORT

A 69-year-old female patient, weighing 58 kilograms and measuring 155 cm in height, presented to our outpatient clinic with back pain following a fall while walking. Her medical history included menopause at age 55 years, prior fractures of the ankle and heel, and a rib fracture a year later. She also had a history of asthma, for which she used prednisolone 16 mg daily for approximately 20 days per month during exacerbations.

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Upon admission, a physical examination revealed localized pain in the upper lumbar region upon palpation. The neurological examination was intact. Radiological evaluation, including preoperative X-ray and computed tomography (CT) scans (Figures 1 and 2) revealed a lumbar vertebrae 1 (L1) compression fracture with approximately 75% loss of vertebral body height.

Further imaging via incorporating sagittal thoracic vertebrae 1-weighted, T2-weighted, and Short Tau Inversion Recovery sequences (Figure 3), confirmed the presence of an acute fracture (white arrow).

Given the degree of vertebral collapse and the patient's symptomatic presentation, an L1 kyphoplasty procedure was planned under sedation. During the operation, balloon expansion successfully achieved significant vertebral augmentation. Postoperative CT imaging revealed a restoration of vertebral body height of approximately 5-8 mm (Figure 4). The patient tolerated the procedure well, with no perioperative complications.

This case underscores the efficacy of kyphoplasty in treating acute vertebra plana and highlights its role in improving vertebral stability and alleviating pain in patients presenting a significant vertebral body collapse.

## DISCUSSION

Vertebra plana represents a severe form of vertebral compression that poses distinct challenges for both diagnosis and management. Traditional conservative approaches remain the cornerstone of treatment for asymptomatic cases or those with minimal functional compromise (3, 4). However, in symptomatic patients, the presence of significant

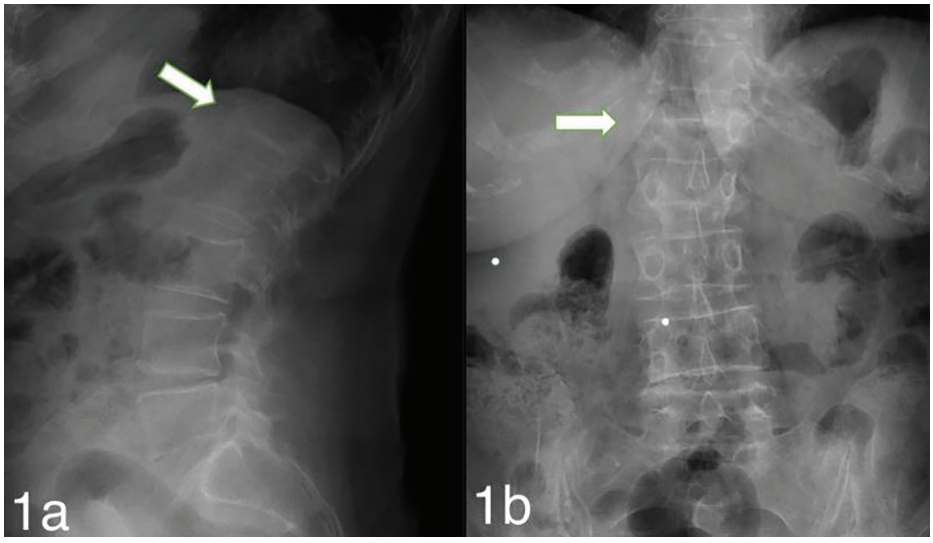


**Figure 1:** a) Preoperative lateral X-ray, b) Preoperative anteroposterior X-ray.

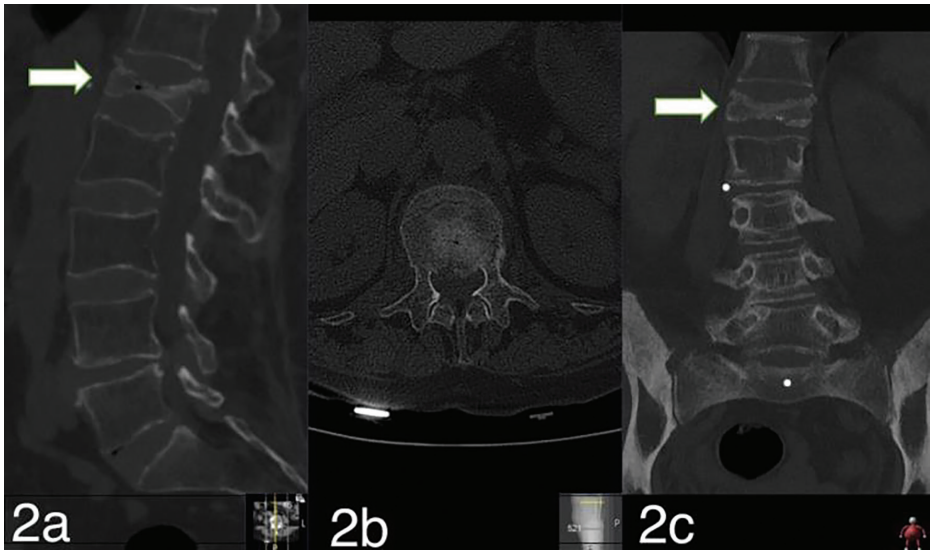


**Figure 2:** a) Preoperative sagittal computed tomography, b) Preoperative axial CT, c) Preoperative coronal CT.
CT: Computed tomography

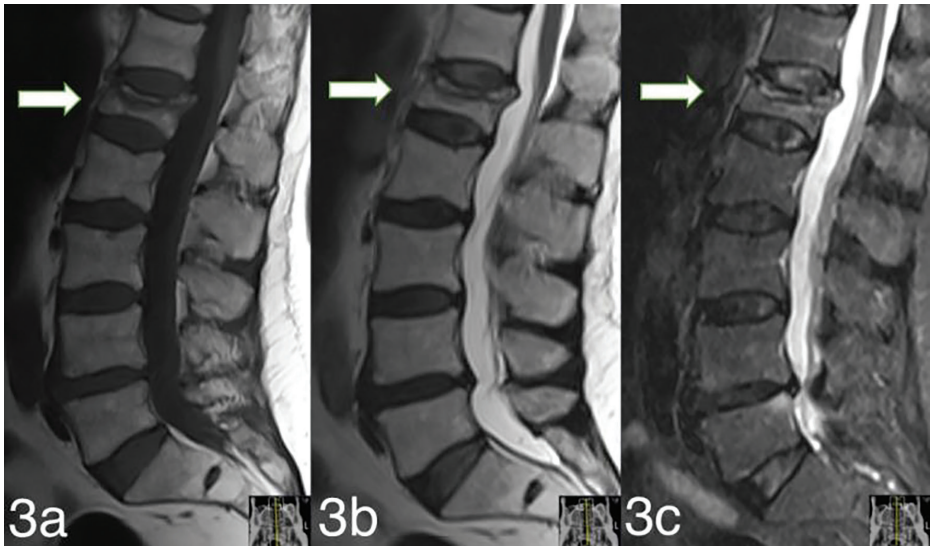


**Figure 3:** a) Preoperative sagittal MRI T1-weighted, b) Preoperative sagittal MRI T2-weighted, c) STIR sequences.
MRI: Magnetic resonance imaging, STIR: Short Tau Inversion Recovery, T1: Thoracic vertebrae 1, T2: Thoracic vertebrae 2

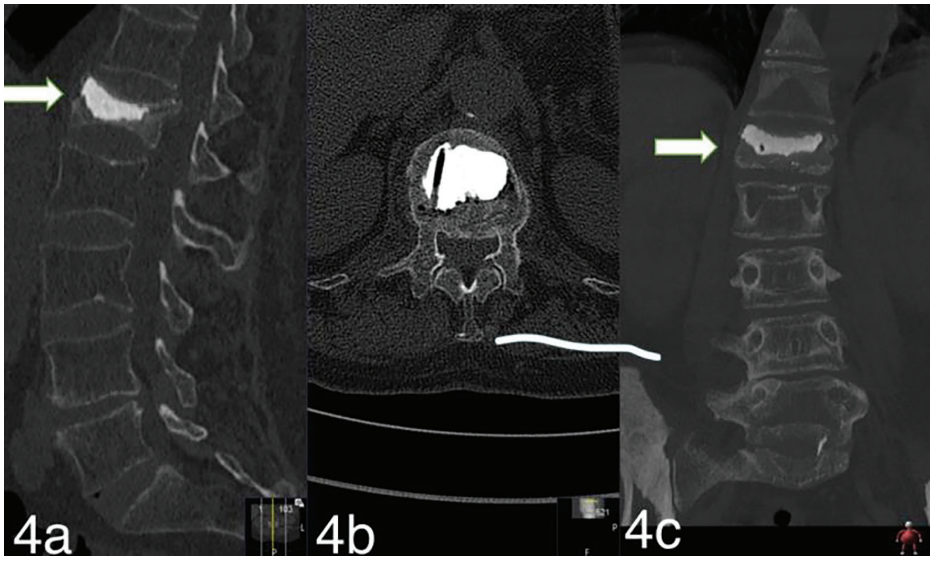


**Figure 4:** a) Sagittal CT, b) Axial CT, c) Coronal CT.
CT: Computed tomography

pain and deformity necessitates surgical intervention to achieve therapeutic objectives, including pain relief, vertebral stabilization, and prevention of kyphotic deformity (3-5).

Kyphoplasty, although not typically applied, can provide significant benefits when performed by experienced surgeons using the correct surgical technique in cases of severe osteoporotic vertebral compression fractures such as vertebra plana. This technique enables vertebral height restoration and stabilization while minimizing perioperative risks. In this patient, a height restoration of 5-8 mm was achieved, highlighting the potential of kyphoplasty to mitigate complications associated with severe vertebral collapse (6). Balloon-assisted augmentation involves inflating a balloon within the vertebra to compress and strengthen the vertebral wall, thereby facilitating the restoration of vertebral height. This method allows for more controlled and symmetrical restoration, contributing to improved clinical outcomes (6).

The impact of long-term corticosteroid use on the pathogenesis of vertebral fractures cannot be overlooked. Chronic prednisolone therapy, as seen in this case, is known to exacerbate bone density loss, increasing the risk of fractures (2). This underscores the importance of comprehensive management strategies, including osteoporosis prophylaxis and fracture risk assessment in such patients (4). This patient's history of prior fractures further illustrates the cumulative impact of comorbidities and chronic medication use on skeletal health.

Despite the promising results achieved with kyphoplasty, the potential for complications, such as cement leakage or insufficient height restoration, warrants careful preoperative evaluation and meticulous intraoperative technique (3, 5). Moreover, patient selection remains pivotal, as advanced vertebra plana cases with concurrent osteonecrosis may exhibit suboptimal outcomes with this approach (6).

## CONCLUSION

In conclusion, kyphoplasty is a valuable intervention for patients with acute vertebral plana, offering significant improvements in vertebral height, pain relief, and functional outcomes. This case emphasizes the necessity for an individualized approach in managing vertebral compression fractures, considering the severity of the collapse, patient comorbidities, and potential surgical risks to achieve optimal therapeutic results.

***Ethics***

***Informed Consent:*** *Written informed consent was obtained from the patient for this study.*

***Footnotes***

***Conflict of Interest:*** *The authors declared no conflict of interest.*

***Author Contributions:*** *Concept: K.A., Y.K., M.C.E., A.T.A., Design: K.A., Y.K., Data Collection or Processing: K.A., M.C.E., Analysis and/or Interpretation: K.A., Y.K., M.C.E., Literature Search: K.A., Y.K., A.T.A., Writing: K.A., Y.K., M.C.E., A.T.A.*

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CASE REPORT

# A RARE CASE OF ISOLATED SOLITARY PULMONARY METASTASIS OF PROSTATE CARCINOMA

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## ABSTRACT

Prostate cancer is the fourth most diagnosed cancer and the eighth leading cause of cancer-related mortality globally. Although distant metastases of prostate cancer are common, isolated pulmonary metastasis is exceptionally rare, occurring in fewer than 1% of cases. We present the case of a 61-year-old male who was diagnosed with extraprostatic highly invasive prostate adenocarcinoma in 2011, at the age of 49. He had a high prostate-specific antigen level of 41 ng/mL and a Gleason score of 7 (4+3), placing him in the intermediate-risk category (grade group 3). Following a radical prostatectomy, external iliac and pelvic lymphadenectomy, the patient was regularly monitored. Twelve years later, during routine follow-up and restaging, a Gallium-68 prostate-specific membrane antigen positron emission tomography computed tomography scan revealed a 2 cm nodular lesion in the upper lobe of the left lung, which was identified as a metastasis of prostate cancer. Histopathological analysis following surgical resection confirmed the diagnosis of isolated lung metastasis of prostate cancer. To the best of our knowledge, this is only the second reported case of singular pulmonary metastasis of prostate cancer in Türkiye. This case highlights the rarity of isolated pulmonary metastasis in prostate cancer, which occurs in fewer than 1% of cases. Despite the absence of elevated high prostate-specific antigen levels, long-term follow-up and routine imaging are essential for detecting distant metastases in prostate cancer patients. This case underscores the need for careful monitoring and imaging of prostate cancer patients during long-term follow-up, even in the absence of elevated prostate-specific antigen levels, to detect unusual metastatic sites like isolated pulmonary metastasis.

**Keywords:** Lung metastasis, prostate cancer, prostate-specific antigen

## INTRODUCTION

Prostate cancer (PCa) is the fourth most common cancer worldwide and has the eighth highest mortality rate among all cancer types. The age-standardized incidence rate in men is 29.4 per 100,000, and the mortality rate is 7.3 per 100,000 (1). PCa is classified into four main types: ductal adenocarcinoma, prostatic intraepithelial neoplasia-like carcinoma, treatment-related neuroendocrine prostate carcinoma, and adenoid cystic (basal cell) carcinoma of the prostate (2). These different types can show varying metastatic patterns, with bone metastases being the most frequently observed in the majority of cases. However, the metastatic behavior and organ involvement can depend on the subtype of the cancer, making each case unique (3).

Prostate cancer typically metastasizes to the bones, particularly the spine, pelvis, and ribs, due to its affinity for hematopoietically active red bone marrow. Additionally, the cancer cells shedding from the primary tumor site can occasionally form clusters in the bloodstream, adhere to the vascular endothelium, and break apart to reach distant organs. However, most of these cells are susceptible to apoptosis or fail to establish a conducive microenvironment in the target organs, which significantly reduces the likelihood of distant metastases, such as to the lungs, especially in early stages (3). Therefore, pulmonary metastasis from PCa is a relatively rare occurrence, generally manifesting in the advanced stages of the disease. Pulmonary involvement in metastatic PCa has been observed in over 40%

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of autopsy studies. However, isolated lung metastasis is very uncommon, occurring in less than 1% of cases (4).

Isolated lung metastasis from PCa remains an exceptionally rare clinical presentation. To date, only one case has been reported in Türkiye, with the current case potentially being the second documented instance in the literature (5). This case report aims to present a rare occurrence of PCa with isolated lung metastasis and highlights the importance of individualized follow-up strategies for PCa patients. The early detection of metastases in unusual sites, such as the lungs, emphasizes the need for tailored approaches in patient monitoring and management.

## CASE REPORT

In this case, we present a 61-year-old male with a 20 pack-year smoking history. When he was 49 years of age, the patient presented to an external hospital with urinary symptoms, and his prostate-specific antigen (PSA) level was measured at 41 ng/mL (normal: <4 ng/mL, high risk of PCa) and prompted his referral to Trakya University Faculty of Medicine for further evaluation in 2011. The patient initially underwent a prostate biopsy, which revealed prostate adenocarcinoma with a Gleason score (GS) of 7 (3+4), grade group 2. Subsequently, the patient underwent radical prostatectomy (RP) with curative intent, including the removal of right and left obturator, right external iliac and pelvic lymph nodes. No evidence of distant metastasis was detected at that time. The primary tumor involved both lobes of the prostate and had extraprostatic spread. However, no evidence of seminal vesicle invasion or tumor involvement in the spermatic cord was observed. Based on the RP findings, the patient was diagnosed with extraprostatic highly invasive prostate adenocarcinoma with a total GS of 7 (4+3), grade group 3, classified as intermediate risk and staged pathologically as pT3aN0. He ceased smoking and was regularly followed up by medical oncology and thoracic surgery departments between 2011 and 2016, during which no complications or issues were detected, and normal PSA values followed.

In 2017, three months earlier, the patient's PSA level was measured at 0.9 ng/mL (normal: <0.2 ng/mL after prostatectomy). Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) revealed involvement of the left internal iliac lymph node, which was evaluated as lymph node metastasis. Subsequently, lymphadenectomy was performed, revealing sinus histiocytosis-type reactive hyperplasia in two lymph nodes, with no epithelial cells detected on pan-cytokeratin staining. The patient underwent androgen deprivation therapy with goserelin acetate [luteinizing hormone–releasing hormone (LHRH) agonist] in 2018.

Given the return of the disease and the presence of lymph node involvement, a disease relapse was suspected. PCa typically metastasizes first to regional lymph nodes, bones, or lungs, generally with multiple metastases. The observation of a lung nodule in 2023, after lymphadenectomy, raised concern for a possible isolated pulmonary metastasis, which warranted further investigation. The head, neck, mediastinum, thorax, abdomen, and pelvis were assessed using Gallium (Ga)-68 PSMA PET/CT for restaging. A 2-cm nodular lesion showing increased Ga-68 PSMA metabolic activity was detected in the upper lobe of the left lung, which could not be definitively classified as primary lung cancer or PCa metastasis (Figure 1).

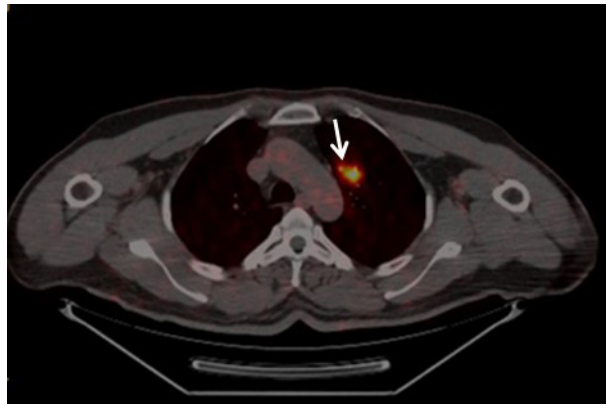

**Figure 1:** A Gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography scan of the patient performed in 2023 for restaging, showing an isolated metastasis to the left lung (arrow) with increased metabolic activity.

After the observation of the nodule, the case was discussed at the oncology council. While PCa typically spreads through regional lymph nodes or to the bone tissue, metastasis via hematogenous dissemination was considered in this case (3). The lung nodule observed prompted a more detailed investigation into potential isolated pulmonary metastasis, and surgery was planned based on the assessment that malignancy was the primary consideration. The patient underwent left upper lobe anterior segmentectomy and mediastinal lymphadenectomy. Lymph nodes numbered 5, 6, 7, 8, 9, 10, and 11 were sampled. The drain was removed on the second postoperative day, and the patient was discharged on the third postoperative day following surgery.

The resected material from the upper lobe of the lung had a stapled margin measuring 13x11.6 cm on its outer surface and had a mottled and anthracotic appearance. When the stapler line was opened and serial sections were taken, a tumor was measured 1.4x1.5x1.6 cm in size with an off-white color and hard consistency. The tumor's distal surface appeared adjacent to the pleura, and the entire tumor was sampled. In lymph node number 8, yellow-colored soft tissues were identified, and no lymph node was observed. Tumor-negative fibroadipose tissue was detected. Other lymph nodes showed soft tissues with an anthracotic appearance, which exhibited signs of hyperplasia and anthracosis.

Immunohistochemical analysis revealed PSA (+), NK3 Homeobox 1 (NKX3.1) (+), Cytokeratin 7 (CK7) (-), Cytokeratin 20 (CK20) (-), Alpha-Methylacyl-CoA Racemase (AMACR) (+), and Thyroid Transcription Factor-1 (TTF-1) (-). These findings are all consistent with PCa lung metastasis (Figures 2-5).

Postoperatively, Ga-68 PSMA metabolic activity was confirmed to be due to isolated lung metastasis of PCa. The patient is currently being followed up regularly with PSA levels within the normal range and with no complaints and treatment.

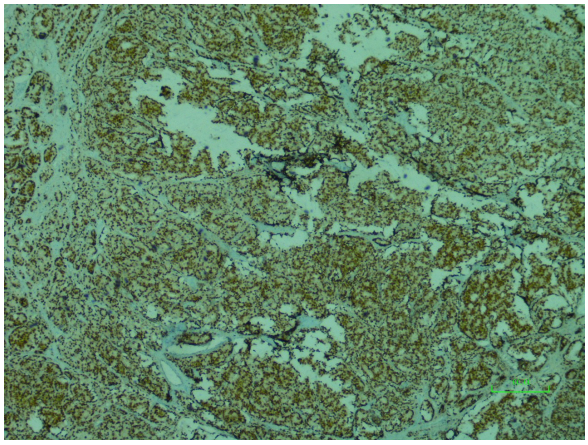

**Figure 2:** NK3 Homeobox 1 (+): Supporting the diagnosis of prostate cancer metastasis.

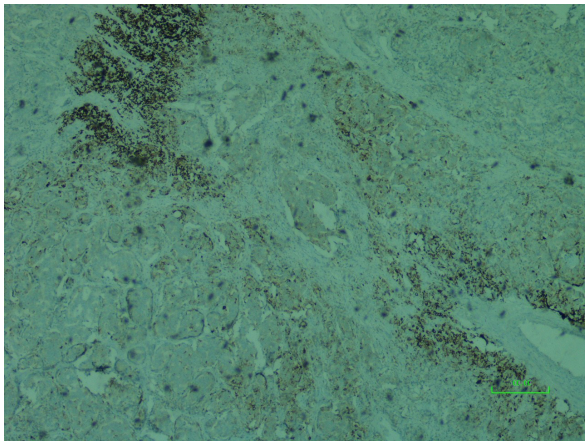

**Figure 3:** Alpha-Methylacyl-CoA Racemase (+): Overexpressed in prostate cancer.

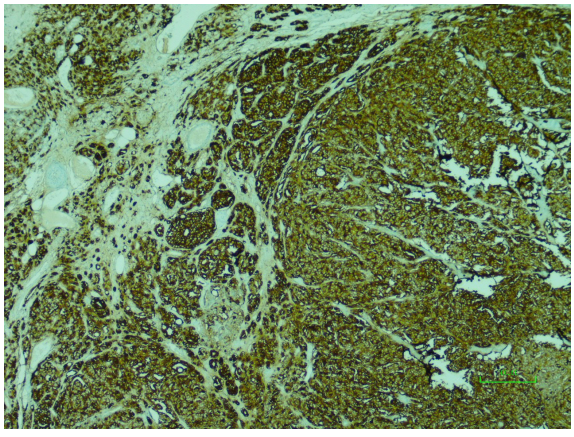

**Figure 4:** Prostate-Specific Antigen (+) represents prostate cancer-originated metastasis.

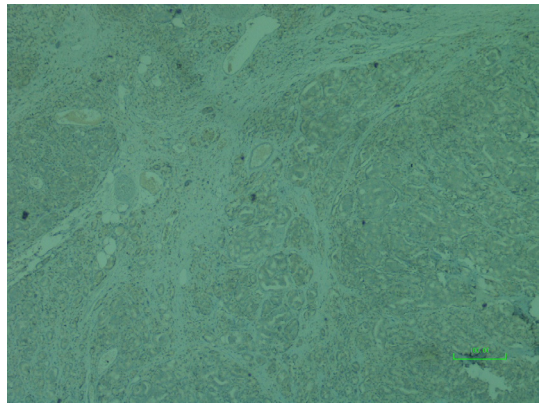

**Figure 5:** Thyroid Transcription Factor-1 (+) excludes primary lung cancer.

## DISCUSSION

Prostate cancer is the fourth most commonly diagnosed malignancy worldwide, following breast, lung, and colorectal cancers, and accounts for approximately 7.3% of all cancer cases (1). The clinical progression and prognosis of PCa are significantly influenced by the presence and distribution of metastases. Bone is the most common site of metastatic involvement, particularly the spine, pelvis, and ribs, due to the affinity of PCa cells for hematopoietically active bone marrow.

Although pulmonary metastasis may occur in advanced stages, isolated lung metastasis without concurrent bone or lymph node involvement is exceedingly rare, reported in fewer than 1% of cases (3, 4). Despite autopsy studies showing lung involvement in up to 40% of patients with metastatic PCa, these typically co-occur with other systemic metastases.

Localized PCa often remains asymptomatic in its early stages and is commonly detected through PSA testing, digital rectal examination (DRE), and imaging modalities such as magnetic resonance imaging and transrectal ultrasound. However, in rare scenarios where patients present with atypical findings such as a solitary pulmonary lesion and normal PSA levels, diagnosis may be delayed or misdirected, underscoring the importance of histopathological confirmation and immunohistochemical profiling (6).

Maru et al. (7) reported a case of a 77-year-old ex-smoker with a solitary pulmonary nodule and normal PSA levels. The case was initially suspected to be primary lung cancer because primary lung cancers are typically singular, while PCa metastases usually present as multiple lesions. Their review of 23 cases of isolated lung metastasis from PCa indicated that normal PSA levels were found in 73% of cases, suggesting that isolated lung metastasis may occur even in the absence of elevated PSA levels, so in some rare cases PCa may metastasize without a significant rise in PSA levels. This highlights the limitations of PSA monitoring and emphasizes the need for additional imaging or molecular markers to detect hidden metastases. Aside from PSA testing, different immunohistochemical markers are used for diagnosis in the resected material. Notably, PSA expression is observed, and while the sensitivity of AMACR is inconsistent,

it is considered significant in the context of PCa, showing an increase. Additionally, NKX3.1 has shown near 100% sensitivity in some studies for PCa (8). In the differential diagnosis of adenocarcinomas, particularly in cases where TTF-1 is negative or the primary is unknown, several markers are utilized. These include Paired Box Gene 8, GATA Binding Protein 3, Caudal Type Homeobox 2, CK7, CK20, and, for male patients, PSMA or NKX3.1 (9). In our case, the immunohistochemistry results indicated PCa metastasis rather than a primary lung tumor.

Extraprostatic highly invasive tumors have a higher potential of recurrence. If PSA's time of doubling is more than one year and the pathological grade is lower than 4, as in our case, possible recurrence may be low (10). However, our patient had lymph node metastasis six years after RP. For this cause, androgen deprivation therapies like LHRH agonists and antagonists were used for our patient, which are commonly used as a systemic treatment for reducing the symptoms and risks of consequences of the disease, such as compression of the spinal cord or pathological fractures (6, 10). Additionally, Ciriaco et al. (11) examined the effectiveness of lung resection surgery in 9 patients with isolated lung metastasis following RP between 2011 and 2017. Four of these patients had solitary lung nodules, while five had multiple nodules. Notably, except for one patient who had both multiple nodules and bone metastasis (and received adjuvant therapy), the remaining patients were free of recurrence for up to 23 months following surgery. This study demonstrates that lung resections may be a viable treatment option even without the use of adjuvant therapy, although further research is needed given the limited number of cases (11). In our case, the patient had a history of smoking cessation 12 years prior, after RP, and he had PCa metastasis to the left lung with normal PSA levels. Unlike the cases presented by Maru et al. (7) and Ciriaco et al. (11), our patient exhibited a solitary tumor in the left upper lung, which was confirmed to be a metastasis from PCa. This case highlights the need for vigilance in the detection of isolated lung metastasis, even when PSA levels remain normal, and reinforces the rarity of this clinical presentation.

Regular PSA monitoring and DREs are crucial for tracking PCa recurrence. Incorporating routine imaging and prostate biopsies into surveillance protocols can significantly enhance early detection of both local recurrence and distant metastases (12). According to a 16-year follow-up of the European Randomized Study of Screening for PCa, PCa-related mortality decreases with long-term follow-ups. The study used PSA values to assess the risk, and as mentioned, a one-time screening may be ineffective in reducing mortality rates. Therefore, for patients with a history of PCa, regular follow-ups and screenings are crucial for disease management, as most patients have asymptomatic metastases (13). Mahmoud et al. (14) examined PCa lung metastasis in a literature review, analyzing a total of 58 studies. They found that most cases were asymptomatic. Only 13 of the studies reported general symptoms related to urinary and pulmonary systems, while 45 studies observed no symptoms at all (6). In our case, the metastatic nodule likely caused pulmonary symptoms such as abnormal phlegm, chest pain, and nonspecific lymphadenitis.

Our case represents one of the rare documented examples of isolated lung metastasis from PCa in Türkiye. To the best of our knowledge, a previously reported case in the country had high levels of PSA and carcinoembryonic antigen (CEA). The patient's CEA level was 529 ng/mL (normal range: <3 ng/mL), and the PSA level was 7.5 ng/mL (normal range: <4 ng/mL). This patient experienced remission of cancer five years after RP. In contrast, our patient developed isolated lung metastasis 12 years postoperatively with normal PSA and CEA levels, and the immunohistochemical profile was unique, showing PSA (+), NKX3.1 (+), CK7 (-), CK20 (-), AMACR (+), and TTF-1 (-) (5). Additionally, a similar case in the country involved a solitary nodule in the lung and brain metastasis without lymph node or bone involvement, further highlighting the diverse metastatic patterns of PCa (15).

## CONCLUSION

In conclusion, these differences emphasize the variability in clinical presentation and immune response in PCa metastasis, suggesting that PSA and CEA levels, while informative, are not always reliable indicators of metastatic progression, especially in cases with normal serum markers. Since such metastases are often asymptomatic, long-term follow-up and advanced imaging are crucial for detecting late recurrences. This case underscores the need for routine imaging beyond PSA monitoring in post-prostatectomy patients. Our findings highlight the necessity of continuous surveillance, even in cases initially considered curative, to improve patient outcomes and disease management.

***Ethics***

***Informed Consent:*** *Written informed consent was obtained.*

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***Footnotes***

***Conflict of Interest:*** *The authors declared no conflict of interest.*

***Author Contributions:*** *Surgical and Medical Practices: F.Y., Concept: F.Y., Design: I.Ç., E.M., Data Collection or Processing: I.Ç., E.M., Analysis and/or Interpretation: I.Ç., E.M., F.Y., Literature Search: I.Ç., E.M., Writing: I.Ç., E.M., F.Y.*

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

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