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Clinical challenges of paraneoplastic endocrine metabolic syndromes

Srushti Shankar, Sumal S. Sundar, Madhumati S. Vaishnav, Leena Lekkala, Chandraprabha Siddalingappa, Kavitha Muniraj, Thummala Kamala, Reshma B. Vijay, Vasanthi Nath, Mandyam D. Chitra, Pushpa Ravikumar, Siddartha Dinesha, Tejeswini Deepak, Srikanta Sathyanarayana *

Samatvam Diabetes Endocrinology and Medical Centre, Samatvam: Science and Research for Human Welfare Trust, Bangalore, India

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ABSTRACT

Background/objective: Paraneoplastic endocrine metabolic syndromes are rare, but clinically significant manifestations of underlying malignancies, often complicating clinical course and impacting treatment outcomes.
Case presentation: Four different paraneoplastic syndromes manifested in an 81-year-old female with metastatic carcinoma rectum, presenting with generalized weakness, inability to walk, severe pain, and low-grade fever.
Discussion: Endocrine metabolic paraneoplastic syndromes can impact prognosis and even be confused as metastatic spread or another "non-existent" clinical entity. They can precede, occur concomitantly or present at later stage of tumour development.
Conclusion: Recognition of these diverse clinical manifestations improves clinical outcomes (earlier cancer diagnosis, better quality of life, optimal tumour-directed therapy or decision towards non-aggressive focussed palliative care).

1. Paraneoplastic Hyponatremia: Hyponatremia (127, 129), with elevated urine sodium, suggestive of inappropriate antidiuretic hormone (ADH) secretion, was treated with fluid restriction, liberal salt intake, 3 % intravenous saline, oral sodium bicarbonate and tolvaptan and tapentadol.
2. Paraneoplastic Leukemoid Reaction: Progressively severe leukocytosis [29960, 36670, 44130, 58450 cells/mm3; with neutrophilia and absence of evidence for infectious/leukemic etiology; procalcitonin = 0.083 ng/mL (<0.1)], was attributed to granulocyte macrophage colony-stimulating factor (GM-CSF) secretion from neoplasm, and empirical antibiotic coverage was provided.
3. Paraneoplastic Hypokalemia: Hypokalemia (2.9, 3.0), likely due to intracellular potassium uptake (in vivo/in vitro) by rapidly proliferating leukocytes and primary/metastatic neoplastic cells (ectopic ACTH secretion ruled out) was treated with intravenous/oral potassium supplementation.
4. Paraneoplastic Fever: Cytokine release from tumor cells or infiltrating immune cells was implicated in the development of fever.

1. Introduction

Paraneoplastic syndromes encompass a diverse array of manifestations that arise secondary to the presence of an underlying malignancy. Paraneoplastic Endocrine Syndromes (PES) encompass a diverse array of clinical manifestations resulting from "ectopic" production of peptide hormones or non-peptide agents by "non-endocrine" neoplastic cells. Dimitriadis et al. (2017) provide a comprehensive review of PES, categorizing them into three main groups based on the secretion of peptide hormones and non-peptide agents [1]. This classification system aids in understanding the pathophysiology and guiding clinical management in patients with these complex conditions.

Group A: Common PES secondary to the secretion of peptide

* Corresponding author. Samatvam Diabetes Endocrinology and Medical Center, Samatvam: Science and Research for Human Welfare Trust, "Jnana Sanjeevini": 2, 1 A Cross Marenahalli, JP Nagar Phase 2; Bangalore, 560078, India.
E-mail address: samatvam@gmail.com (S. Sathyanarayana).

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hormones: They include: 1. Paraneoplastic Hypercalcemia: Hypercalcemia is mediated by parathyroid hormone-related protein (PTHrP) produced by tumors. 2. Paraneoplastic Syndrome of Inappropriate Anti-Diuretic Hormone Secretion (SIADH): Ectopic ADH production leads to euvolemic dilutional hyponatremia. 3. Paraneoplastic Cushing's syndrome (CS): CS arises from ectopic secretion of adrenocorticotropic hormone (ACTH) or corticotropin-releasing hormone (CRH). 4. Paraneoplastic Hypoglycemia: Hypoglycemia results from tumor production of insulin-like growth factors (IGFs) or insulin. 5. Paraneoplastic Acromegaly: Acromegaly can be caused by secretion of growth hormone releasing hormone (GHRH), or occasionally, by an extra-pituitary source of growth hormone (GH).

Group B: Less Common PES secondary to the secretion of peptide hormones: They include: 1. Ectopic renin secretion: Tumors may produce renin, leading to hypertension and electrolyte disturbances. 2. Ectopic β-human chorionic gonadotrophin (beta hCG production): Neoplasms can secrete beta-human chorionic gonadotropin (β-hCG), posing diagnostic challenges. 3. Ectopic gonadotrophin production: Ectopic production of gonadotropins (luteinising hormone, follicle stimulating hormone) by tumors can result in reproductive hormone imbalances and clinical manifestations. 4. Other ectopic pituitary hormone secretion: Various tumors may ectopically secrete other pituitary hormones (thyrotropin, prolactin), contributing to endocrine disturbances and clinical complexities. 5. Ectopic gut hormone secretion: Tumors can produce gut hormones, leading to gastrointestinal symptoms and metabolic abnormalities. 6. Ectopic calcitonin hypersecretion: Ectopic secretion of calcitonin by tumors can result in hypocalcemia and neuroendocrine tumor syndromes. 7. Tumor-induced osteomalacia: Certain tumors produce fibroblast growth factor 23 (FGF23), causing renal phosphate wasting and osteomalacia. 8. Hypertrophic osteoarthropathy: Hypertrophic osteoarthropathy may occur secondary to neoplastic conditions, resulting in joint pain and periostitis. 9. Ectopic oxytocin secretion: Tumors may ectopically secrete oxytocin, leading to hyponatremia and neuroendocrine manifestations. 10. Ectopic atrial natriuretic peptide secretion: Ectopic secretion of atrial natriuretic peptide (ANP) by tumors can result in volume overload and cardiac dysfunction. 11. Ectopic human placental lactogen secretion: Some tumors produce human placental lactogen (hPL), leading to gestational hormone-like effects and metabolic disturbances. 11. Ectopic cholecystokinin secretion: Tumors may ectopically secrete cholecystokinin (CCK), causing gastrointestinal symptoms and pancreatic enzyme secretion.

Group C: Endocrine paraneoplastic syndromes secondary to the secretion of non-peptide agents: They include: 1. Paraneoplastic cytokines secretion: Tumors can produce cytokines, contributing to systemic inflammation and metabolic dysregulation. 2. Paraneoplastic steroid hormone secretion: Some tumors ectopically secrete steroid hormones, leading to endocrine disturbances and clinical manifestations. 3. Paraneoplastic hyperaldosteronism: Paraneoplastic hyperaldosteronism may arise from aldosterone-producing tumors, causing hypertension and electrolyte imbalances. 4. Struma ovarii: Struma ovarii refers to the presence of thyroid tissue within an ovarian teratoma, leading to thyroid hormone production and clinical sequelae.

In this manuscript, we try to describe the clinical complexity posed by paraneoplastic endocrine metabolic syndromes, utilising the illustration of an elderly lady with a non-endocrine malignant neoplasm, who manifested four such "ectopic" endocrine metabolic dysfunctions.

2. Case Presentation

In 2021, an 81-year-old female with history of hypertension was diagnosed with carcinoma rectum. She underwent surgery, colostomy, chemotherapy, and radiotherapy. By 2023, she was under palliative care due to progressive metastatic malignancy involving the liver, lungs, and bones. In August 2023, she was admitted to the hospital with generalized weakness, inability to walk, severe pain, and fever (99–102.2 F) persisting for 10 days. During her complicated terminal clinical course, she developed multiple paraneoplastic endocrine manifestations, which are briefly summarised here (Table 1).

A: Paraneoplastic Hyponatremia: S Sodium = 127, 129, 129, 137, 134 mmol/L (134–145); Spot urine sodium = 65 mmol; S Uric acid = 3.5 mg/dL (4.4–7.6); S Cortisol 8 a.m. = 15.5 (6.7–22.6); T3 total = 0.34 ng/mL (0.97–1.69), T4 total = 6.87 mcg/dL (5.5–11), TSH = 1.87 mIU/mL (0.46–4.68); LH = 0.35 mIU/mL (16–54); FSH = 1.9 mIU/mL (23–116); S calcium = 8.9 mg/dL (8.4–10.2); S Phosphorus = 2.31mg/dL (2.5–4.5). Diagnosis: Possible paraneoplastic ADH secretion/SIADH; pain/narcotics-induced hypothalamic ADH secretion. Treatment: Fluid restriction, liberal salt intake, 3 % saline, oral sodium bicarbonate, tolvaptan, and tapentadol for pain management.

B: Paraneoplastic Leukemoid Reaction: Total leukocyte count = 29960, 36670, 44130, 58450 cells/mm3 (4000-11,000); Differential count: Neutrophils = 85–94 %; Lymphocytes = 10-4 %. CRP = 93.7, 24.0 mg/dL (<0.3); Procalcitonin = 0.097, 0.083 ng/mL (<0.1). Ruled out significant sepsis; no obvious laboratory or imaging evidence of any infectious or leukemic etiology (Repeated serial evaluations and reviews by specialist clinical haematologist – oncologist and hematopathologist). Diagnosis: Paraneoplastic leukemoid reaction. Treatment: Empirical antibiotic coverage.

C: Paraneoplastic Hypokalemia: S Potassium = 3.3, 3.4, 3.7, 2.9, 3.0 mmol/L (3.5–5.1). Diagnosis: Hypokalemia likely due to (in vivo and in vitro) intracellular potassium uptake by rapidly proliferating leukocytes (and primary and metastatic neoplastic cells). Ectopic ACTH secretion ruled out (Serum cortisol and plasma ACTH within the normal ranges). Treatment: Intravenous and oral potassium supplementation.

D: Paraneoplastic Fever: The patient's fever was attributed to cytokine release syndrome, likely mediated by tumor necrosis factor and interleukin-1.

In view of the terminal nature of the illness, the family chose continued palliative care at home, where she died 2 weeks after discharge from hospital.

3. Discussion

PES syndromes can precede, coexist with, or manifest at later stages of tumor development. Recognition of these syndromes is crucial as they can mimic metastatic spread or other clinical entities, leading to diagnostic and therapeutic challenges.

A: Paraneoplastic Hyponatremia: The pathogenesis of paraneoplastic hyponatremia is multifactorial and may involve various mechanisms, including direct tumor secretion of ADH or its precursor, tumor-induced ectopic production of vasopressin-releasing factors, or altered osmoregulation due to systemic inflammation or chemotherapy-induced electrolyte disturbances [2–4]. Management of paraneoplastic hyponatremia revolves around correcting the underlying cause while carefully monitoring serum sodium levels to prevent overcorrection, which can lead to osmotic demyelination syndrome. Treatment strategies include fluid restriction, hypertonic saline infusion, and pharmacological agents such as vaptans, which selectively antagonize the action of ADH receptors.

B: Paraneoplastic Leukemoid Reaction: Paraneoplastic leukemoid reaction (PLR) is characterized by extreme leukocytosis (usually >40,000 cells/mm^3) in the absence of a primary hematological disorder. PLR is due to release of leukocyte growth factors such as G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-6 (IL-6) by tumor cells. These cytokines stimulate the bone marrow to produce excessive numbers of neutrophils, leading to leukocytosis [5–10]. Diagnosis of PLR requires exclusion of other causes of leukocytosis, including infection, inflammation, and hematological malignancies. Management involves treating the underlying malignancy and symptomatic management of leukocytosis, which may include antibiotic therapy if infection is suspected.

C: Paraneoplastic Hypokalemia: Paraneoplastic hypokalemia is a

Table 1
Paraneoplastic Endocrine Metabolic Syndromes: An Illustrative Example (Year 2023): Hyponatremia, hypokalemia, leukemoid reaction and fever (99–102.2 F).

Value	Range	Aug 30	Aug 31	Sep 02	Sep 04	Sep 05	Sep 06
S Sodium	134–145 mmol/L	127	129	129	137	134	132
S Potassium	3.5–5.1 mmol/L	3.3	3.4	3.7	2.9	3.05	3.18
S Uric Acid	3.5–8.5 mg/dL	3.5				3.3	
S Creatinine	0.60–1.3 mg/dL	0.44				0.41	
Hemoglobin	13–17 g/dL	9.85		11.4	10.4		
WBC Total	4000-11,000 cells/mm^3	29,960		36,670	44,130	58,450	
Neutrophils	40–80 %	85		94	94		
CRP	<0.3mg/dL	94				24	
Procalcitonin	<0.1mg/mL	0.097				0.083	

21. S= Serum; CRP= C Reactive Protein.

rare electrolyte abnormality characterized by low serum potassium levels (<3.5 mmol/L) in the absence of renal or gastrointestinal losses. It is often associated with malignancies, particularly those with high cell turnover rates such as leukemia, lymphoma, and small cell lung cancer. Paraneoplastic hypokalemia is thought to involve intracellular potassium uptake by rapidly proliferating tumor cells and leukocytes. Ectopic adrenocorticotropic hormone (ACTH) secretion by tumors, leading to increased mineralocorticoid activity and potassium excretion, may also contribute to hypokalemia in some cases [11–17]. Management of paraneoplastic hypokalemia includes potassium supplementation and treatment of the underlying malignancy.

D: Paraneoplastic Fever: Paraneoplastic fever is a systemic febrile response observed in patients with cancer that is not attributable to an infectious etiology. It is thought to result from the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) by tumor cells or infiltrating immune cells [18–20]. The pathogenesis of paraneoplastic fever involves the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (action of cytokines on the thermoregulatory centers in the hypothalamus). Management of paraneoplastic fever focuses on treating the underlying malignancy and providing supportive care.

4. Conclusion

Endocrine metabolic paraneoplastic syndromes can impact prognosis and even be confused as metastatic spread or another "non-existent" clinical entity. They can precede, occur concomitantly or present at later stage of tumour development. Recognition of these diverse clinical manifestations improves clinical outcomes (earlier cancer diagnosis, better quality of life, optimal tumour-directed therapy or decision towards non-aggressive focussed palliative care).

CRediT authorship contribution statement

Srushti Shankar: Writing – original draft, Methodology. **Sumal S. Sundar:** Writing – original draft, Methodology. **Madhumati S. Vaishnav:** Writing – original draft, Methodology. **Leena Lekkala:** Writing – original draft, Methodology. **Chandraprabha Siddalingappa:** Writing – original draft, Methodology. **Kavitha Muniraj:** Writing – original draft, Methodology. **Thummala Kamala:** Writing – original draft, Methodology. **Reshma B. Vijay:** Writing – original draft, Methodology. **Vasanthi Nath:** Writing – original draft, Methodology. **Mandyam D. Chitra:** Writing – original draft, Methodology. **Pushpa Ravikumar:** Writing – original draft, Methodology. **Siddartha Dinesha:** Writing – original draft, Methodology. **Tejeswini Deepak:** Writing – original draft, Methodology. **Srikanta Sathyanarayana:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Statement of patient consent

The authors attest that they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and regulatory authorities, including patient consent where appropriate.

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Nil.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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