# Paraneoplastic Manifestation of Bladder Cell Carcinoma

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## INTRODUCTION

Paraneoplastic syndromes (PNS) are defined as a collection of symptoms and clinical signs occurring in cancer patients and involving systemic effects taking place remotely from the tumor; they are not related either to its local repercussion or distant spread and are not caused by infection, nutritional deficiency or treatment.

A paraneoplastic phenomenon usually arises from (a) biologically active substances (hormones, hormone precursors, or hormone-like substances) aberrantly produced by the underlying neoplasm, (b) modulation of the immune system via autoimmunity, immune complexes production and immune suppression, (c) unknown causes(1).

The prevalence of low grade papillary carcinoma of the bladder in Nigeria is 5.4%(2), while the commonest histologic pattern seen is squamous cell carcinoma(2,3). This is the case of a 65year old woman with features of peripheral neuropathy; however had an underlying bladder cell carcinoma with low grade papillary carcinoma.

## CASE REPORT

Mrs O.E a 65 year old woman who presented with 1 year history of tingling sensation in both hands and 6 months history of haematuria. She developed paraesthesia with numbness of both hands and feet. There was associated heaviness and weakness with persistent difficulty in holding objects or writing. A few months after, she developed pain in the neck, which was sharp radiates down both hands, with low back pain also that radiates to lower limbs. No associated allodynia. There was 6 month history of painless terminal haematuria, with progressive weight loss, no dysuria, frequency or urgency, or difficulty in passing urine, no leg or facial swelling. No history of exposure to hydrocarbon, mercury containing soaps, snake bite, walking bare-footed in stagnant water, or smoking. She has a 5 years history of hypertension, not a known diabetic.

On examination, she was not pale, anicteric, afebrile, acyanosed, nil pedal oedema. CNS review shows power in both upper limb was 3-, and lower limbs was 5, while tone and reflexes were normal. Pulse rate was 80bpm, BP 110/70mmHg, no raised JVP, Apex was 5$^{th}$ left intercostals space mid-clavicular line $S_1$ and $S_2$ sounds. Abdomen was full moves with respiration, no area of tenderness, no renal angle tenderness or flank fullness, and vaginal examination was normal. Other examination was normal. An initial assessment of cervical spondylitic myeloradiculopathy was made, to rule out urogenital malignancy, and was placed on oral pregabalin.

Urinalysis showed 3+ of protein and 3+ of blood, while urine microscopy showed numerous RBC and pus cells of 10 – 12cells/HPF. Abdominal ultrasound scan showed uniformly filled bladder with multiple irregular edges and echogenic masses with thickened bladder walls. Rt Kidney was 105×39mm and Lt Kidney was 105×41mm with good corticomedullary differentiation, this is as shown in

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Table: Investigations findings included: Cervical MRI was normal.

| Parameters | Result | Parameters | Result |
|---|---|---|---|
| Na | 144mmo/l | $K^+$ | 3.6mmol/l |
| $Cl^-$ | 104.7mmol/l | $PO_4^{2-}$ | 4mmol/l |
| Urea | 18mg/dl | Calcium | 9.43mg/dl |
| Creatinine | 0.8mg/dl | Uric acid | 3.7mg/dl |
| $HCO_3$ | 27.1meq/l | Globulin | 3.32g/dl |
| Total protein | 7.8g/dl | Albumin | 4.84g/dl |
| FBS | 86.6mg/dl | HbA1c | 7% |
| Acid phosphatise | 3.21ng/ml | PCV | 37.2% |
| WBC | $7 \times 10^9$/L | Platelet | $555{,}000 \times 10^3/mm^3$ |
| Prothrombin time | 19secs | INR | 1.3 |
| PTTK | 41secs | | |

Figure 1. Abdominopelvic CT scan showed irregularities in the outline of the bladder, with large filling defects in the posterior wall and multiple fibroid lesions and calcifications. ECG showed sinus tachycardia, and LVH with strain. Cystoscopy revealed left superior and right lateral wall masses in the bladder.

A final diagnosis of bladder cell carcinoma with paraneoplastic syndrome was made. She had

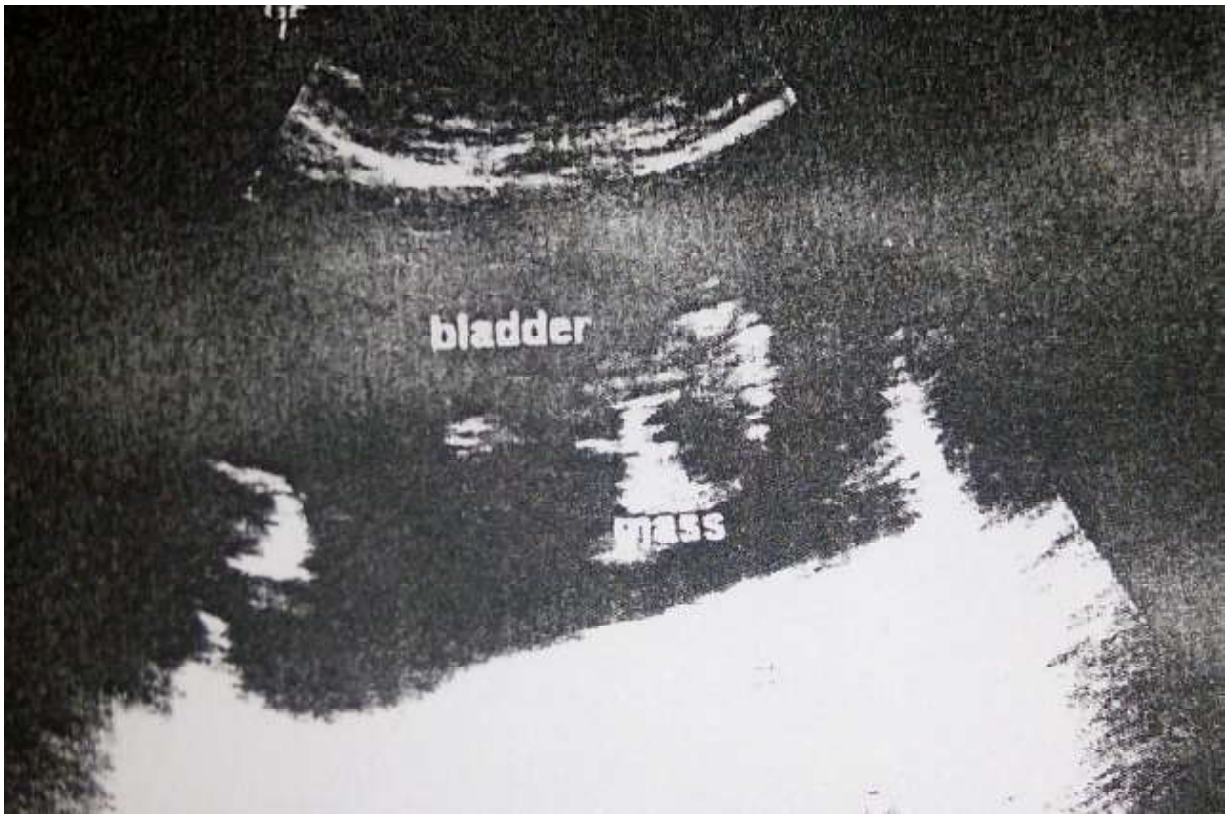


**Fig. 1:** Showing abdomino-pelvic ultrasound scan of the bladder and intravesical mass

Transurethral resection of the bladder tumour, and histology report showed proliferation of malignant urothelial cells, forming papillary structures with fibrovascular core, and malignant cells exhibit high nuclear : cytoplasmic ratio, basophilic cytoplasm and areas of haemorrhage, concluded as superficial low grade papillary urothelial carcinoma. She was commenced on chemotherapy via intravesical instillation of Epirubicin, due to the absence intravesical BCG instillation. The symptoms of peripheral neuropathy spontaneously resolved after initiation of therapy towards the treatment of the bladder cancer, and oral pregabalin was stopped.

## DISCUSSION

To recognize a PNS may be clinically relevant for several reasons: (a) it can lead to the diagnosis of a previously undetected neoplasm; (b) it can dominate the clinical picture and thus lead to errors with respect to the origin and type of primary tumour; (c) it can follow the clinical course of the underlying tumour and thus be useful for monitoring its evolution (neoplastic marker)(1).

This is the case of the index patient who was initially managed for cervical spondylosis and myelopathy, while the cervical MRI ruled out cervical spondylosis, before intensive search and patient was discovered to have bladder cell carcinoma.

Neurological paraneoplastic syndrome (NPNS) affect 6% of all patients with cancer. NPNS sporadically reported in patients with urological tumors. Existing literature have documented the association between peripheral neuropathy as a paraneoplastic manifestation of bladder cancer (1, 4 - 6). There are case reports of association between peripheral neuropathy and bladder cell carcinoma(7, 8)**.** Currently, it is thought that most or all NPNS are immune-mediated. They may be caused by ectopic expression/release of antigens normally confined exclusively in the central nervous system. Some of these so-called onconeural antigens are also expressed in the normal testis, an organ that is, like the brain, an immunologically privileged site. Onconeural antigens are present in the tumour in all patients with antibody-positive NPNS and in many patients without such disorders. The neurological disorder usually appears before the cancer has been identified and develops rapidly. NPNS are usually severe, often disabling, and sometimes lethal. Search for autoantibodies in cerebrospinal fluid (CSF) is very important to confirm the diagnosis and may suggest the site of the underlying cancer. The use of sensitive imaging techniques such as CT and PET combined studies are often required.

Radical treatment of the underlying tumour must be attempted, and the excision of the bladder tumour should be followed by adjuvant intravesical therapy, either with the use of intravesical BCG, or intravesical instillation of chemotherapeutic agents such as epirubicin, mitomycin or doxorubicin to reduce the rate of recurrence(9). Meta-analysis have shown the superiority of intravesical BCG over intravesical epirubicin or mitomycin, while epirubicin and mitomycin have proven similar efficacy more than doxorubicin(9,10). Immunosuppression by intravenous immunoglobulins, steroids, immunosuppressive drugs or by plasmapheresis should be reserved for patients with clearly identifiable antibodies in their serum(11). Although autoantibodies were not sort for in the index patient, cervical MRI ruled out any possibility of compressive myelopathy. While other potential causes of peripheral neuropathy such as syphilis, vitamin B12 deficiency, HIV could have been sorted after, but since the symptoms of peripheral neuropathy spontaneously resolved after the therapy was geared towards bladder tumour, and oral pregabalin was also stopped, we did not consider it essential to continue the search for other causes.

In conclusion, paraneoplastic syndrome can manifest with neurologic symptoms, which can arise earlier before the onset of the underlying malignancy, and over shadow the background malignancy. This can result in unnecessary investigations and mislead an unsuspecting physician. Therefore, high index of suspicion is necessary for early and prompt management.

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