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Letter to the Editor

Role of Autoantibodies in Diagnosis of Paraneoplastic Syndrome in Patients with Cancer

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Case History & Scenario

A 73-year-old Caucasian lady was admitted to a District Generel Hospital in NHS UK. Her primary complaint was poor appetite, self-neglect and low mood for approximately 3-4 months.

She was a widow and had earlier lived as a house wife. She was living a retired life in her own house. She raised 3 sons who were grown up and settled in their own lives. Prio to this episode of illness, she was able to look after herself.

She was admitted to a medical ward. She was initially seen in the Emergency department. She went through initial medical clerking followed by physical examination by the admitting doctor. Her physical examination was reported as grossly normal including abdominal & Pelvic examination. Her BMI was counted as 21.5. Her Height was 5 feet 3 inches(160 cm). Her weight was 55 kg.

Blood showed normal renal functions, normal Liver functions test, normal Thyroid function tests. Bone profile and Electrolyrtes were normal. B12 and folate levels were fine. The inflammatory markers including FBC & CRP were normal. Abdominal & chest X-Ray were normal.

Cognitive examination showed Addenbrookes-3 score of 90/100. She scored well in all modalities of cognition except short term deficits but it was thought to be age related STM loss.

She was initially referred to a dietician who gave her a diet plan. The medical team also referred to the old age Liaison Psychiatry Team. This step was taken to diagnose/treat or rule out possible Depression.

Patient was promptly seen by old age Psychiatry team and after thorough assessment she was started on trial of Antidepressant. It belonged to SSRI group of antidepressant. Her mood was described as low but she had no thoughts of harming self or others.

There was no past history of depression. There was no family history of mental illness. There was no past medical history except high Blood pressure and high cholesterol and she was taking prescribed medications for that. She had no reported allergies.

In the coming days and weeks patients weight continued to drop. The medical team liaised with the Psychiatry team and insisted that patients depression is getting worse. The Medical team was also worried about her poor dietary intake & element of self neglect. Patient needed prompting in self care although quite capable to do self care. Medical team was of the opinion that patient needs inpatient admission to psychiatry ward and might need ECT(Electro-convulsive Therapy) as a last resort if she did not respond to trial of antidepressants.

MDT meeting was called in the medical unit which was attended by medics, psychiatrist, medical nurses, social worker and the representative of family.

The Psychiatric consultant initiated further investigations and requested Paraneoplastic Autoantibody screen as presentation of depression was very odd and there was no apparent psychosocial trigger in this case.

The results came back and ANNA-1(Anti-Neuronal nuclear antibody Type 1) and ANNA-2 autoantibody came surprisingly positive.

After this development Tumor Marker screen was initiated by the medical team. CEA-19 was positive. MRI abdomen and pelvis showed 3 cm mass/tumor in the middle one third part of body of Pancreas. It was suspected to be Adenocarcinoma which is the most common(90 percent) of the cases of Pancreatic cancer.

An MDT(Multi-disciplinary team) meeting was called again and family was briefed about the new diagnosis by the visiting oncologist. Various options of treatment were offered including surgery and radiotherapy but the family was not in favour given patients age, frailty and prognosis. It was suspected that the tumor might have metastasized to the peritoneum as there were clinical signs of peritoneal effusion which was a relatively recent clinical development.
Patient sadly passed away after 6 weeks of initial diagnosis of pancreatic tumor and spent last few weeks in hospice under supervision of the palliative care team.
Following this clinical incident, an internal pathway for older patients was developed who presented with depression, poor appetite and sudden weight loss.
This included the paraneoplastic autoantibody screen and MRI chest, abdomen and pelvis to rule out malignancy.
Pancreatic cancer as such is common in patients over 70 years of age. It occurs more in the western/developed nations. It occurs more in males than females. Smoking, diabetes and obesity are risk factors. 5-10 percent cases are inherited. It is third most common cancer in UK. It is one of the most lethal cancers and 450 thousand patients die every year. The survival rate is 25 percent after a year of diagnosis. 90 percent are Adenocarcinoma which are Exocrine in nature. 5-10 percent tumors are endocrine in nature including rare neuroendocrine ones.

Broader Discussion:
Definition of Paraneoplastic Syndrome:
A Paraneoplastic syndrome is combination of clinical signs and symptoms which happens due to presence of tumor in the body. Tumor is often cancerous with poor prognosis.
The cancer produces certain neurochemical with neuro signalling properties which produces the set of clinical signs and symptoms.
The other mechanism of this interesting clinical phenomenon is production of antibodies by the body against the tumor which it identifies as alien. The signs and symptoms due to local expansion and resultant pressure effects are not part of paraneoplastic syndrome.
Statistics in general:
Occurs in the middle-aged patients(Age>40 years).
Most Common Causes:
- Lungs
- Breast
- Ovaries
- Lymphatic system/Lymphoma.

Signs & Symptoms:
PNS(paraneoplastic Syndrome) affects many organs and systems in the body.
General Symptoms:
Common initial symptoms can be fever which is due to release of cytokines called pyrogens which are produced by lymphocytes(T Cells)
Systemic:
Endocrine Dysfunction:
- Cushings Syndrome
- SIADH(Syndrome of inappropriate Anti-diuretic Hormone
- Hypocalcemia
- Hypoglycemia
- Carcinoid Syndrome(endocrine tumor of gut)
- Hyperaldosteronism.

Neurological System:
Lambert-Eaten Myasthenia Syndrome
*This is a rare autoimmune disorder characterized by muscle weakness of the limbs. It is also known as Carcinomatous mypopathy or Myasthenia Syndrome. This is more commonly related with small cell lung carcinoma. It is result of auto- antibodies against presynaptic voltage gated calcium channels.
Treatment of cancer relieves the system of these autoantibodies. Other treatments include steroids, Azathiopurine (immune suppressant), intravenous immunoglobulin which co-competes with autoantibodies for neuromascular junction.
Plasma exchange is sometimes required. The illness coincides with increasing age (>40 years) with diagnosis of cancer.

Mechanism of Action:
The mechanism of PNS varies although it often coincides with the emergence of tumor often cancerous/malignant in nature. It is manifested by emergence of autoantibodies against the tumor cells to fight off and destroy the tumor tissue which is identified as an alien object. The antibodies are produced as a result of antigens associated response on the surface of tumor cells.
The pathogenesis of PNS(Paraneoplastic syndrome) is hypothesized by interaction of autoantibodies against the normal cells belonging to various tissues.
Diagnossis of Paraneoplastic Syndrome
Diagnosis can be based on the following factors.
Physical Examination:
General & Physical Health Signs
For example, Weight loss, Anemia, Skin Pigmentation, local skin tumor growth, fractures(bone cancer)skin lesions for example papilloma.
Systemic Physical Examination:
- Abdominal Swelling
- Shifting dullness(Fluid in the peritoneal cavity)
- Local Growth
- Neurological signs including numbness & weakness of limb muscles(Brain Tumor)
- Difficulty in breathing/cough with Haemoptysis.

Radiological Investigations:
Based on the site and clinical presentation, following radiological investigations can be indicative of cancerous growth.
X-Ray Chest:
For example, Bowel obstruction for Bowel cancer
:Shadow on Lung X-Ray on consolidation/collapse of a lobe in the lungs.
:Shadow of bone cancer of X-Ray limbs
- Ultrasound Neck for Thyroid cancer/Abdominal/Pelvic cancers
- CT scan (With or without Contrast) of Neck/Thorax/Abdomen/Pelvis
- MRI Scan

Histopathological Investigations:
- Biopsy via CT scan guided probe/endoscopic probe/MRCP (magnetic Resonance Cholangiopancreatography) probe.

Tumor Markers:
A Tumor marker is a biomarker that can be used to indicate the presence of cancer or progression of cancer. It can be either present in tumor calls/produced by tumor cells0 or get secreted in the body fluids. It can be a molecule that is produced by a normal cell in relation to cancer cells.

Examples:
*Prostate Specific Antigen(PSA)
*Alpha Fetoprotein(AFP) for liver cancer
*CA 15-3 for Breast Cancer
* CA 27.29 for Breast Cancer
*CA-19-9 for Malignant Pancreatic or Colorectal cancer
* CA-125 Mainly Ovarian cancer but can be high in other Gynaecological cancers/breast cancer, lung cancer and gastrointestinal cancer.
*CEA(Carcinoembryonic Antigen) Mainly Gastrointestinal cancer, lung cancer, Ovarian cancer, Urinary Tract Cancer
*Lymphocyte Markers for example in Lymphoma & Leukemia

Examples of Autoimmune Antibodies:
In Teratoma which is tumor made up of several types of tissues such as hair, muscle, teeth and bone etc. Teratoma can arise in ovary, testicles or sacrum. Autoimmune reaction against this tumor produces NMDA receptor autoantibodies.

- HU(Anti Neuronal Nuclear antobody ANNA Type 1) and ANNA type 2

These can be found in various tumors including Pancreatic cancers.
YO(Purkinje cell cytoplasmic antibody Type 1 also known as PCA-1)

- CRMP5 (Collapsin response Mediator Protein 5 also known as CV2)
- MA2/TA and Amphiphysin are thought to be diagnostic of cancerous growth.
- Ho and Yu are found in cancers with prevalence of 38 percent and 13.4 percent respectively.
- Ri has 5.1 prevalence
- Ma2/Ta has 4.5 percent and CV2 has 6.5 prevalence in serum auto antibodies PNS profile.
- Ho and Yu and amphiphysin are thought to be diagnostic for PNS in general.
- Ri has 5.1 percent prevalence while Ma2/Ta has prevalence of 4.5 percent. CV2 and Amphipysin has positive diagnostic prevalence in 6.5 and 3.4 percent respectively.
- Yo has male predominance and same applies to Ma2/Ta
- Except for Ma2/Ta all autoantibodies are predominantly found in older adults.
- Multiple autoantibodies can be found in the same patient with cancer.

The neuronal autoantibodies like ANNA-1 and ANNA-2 may target the brain areas responsible for mood & cognition resulting in low mood and cognitive issues with sudden & new onset with no prior history.

Conclusion
The clinical presentation in Pancreatic cancers can be varied. Pancreatic cancer depending on its site of origin can remain silent before producing clinical signs and symptoms.
The paraneoplastic syndrome can complicate the clinical picture. It does it by producing autoantibodies for example Anti Neuronal antibodies type 1 & 2 and CRMPS which may target areas of brain responsible for mood & memory.
It may create false flag sign as patient initially present with low mood and possibly confusion. Apart from Tumor markers and radiological investigations to confirm diagnosis of Pancreatic tumor, the role of serum autoantibodies cannot be ignored in reaching positive predictive probability of cancer diagnosis.
This is especially true like the patient discussed in the case studies who initially presented with low mood with poor appetite.
Further case reports are needed to strengthen the clinical practice of requesting paraneoplastic autoantibody screen in patients with suspicion of abdominal malignancy especially pancreatic carcinoma.

Keywords: Autoantibodies, Paraneoplastic, Cancer

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