I have received speakers honoraria from the following companies: Amgen, Astra-Zeneca, Celgene, Eisai, Ipsen, Roche.

I have requested funds from several companies to support continuing medical education on Vancouver Island (as the chair of the Van Isle Oncology Conference, VIONC).

I participate in clinical trials and some of those trials are sponsored by private companies: Amgen, Celldex.
OBJECTIVES

By the end of this presentation, you should be able to…

- 1) Describe the key features of Paraneoplastic Syndromes (PNS).
- 2) Explain how PNS arise (mechanism).
- 3) Discuss the collection of symptoms seen in relation to a primary tumour.
- 4) Manage the symptoms of PNS in a multidisciplinary team.
PLAN FOR TODAY

- **Introduction**: define paraneoplastic syndrome (PNS)
- **Mechanisms**: the two main mechanisms of PNS demonstrated in two case reports
- **Cases**: discuss common scenarios, what we might see and do
- **Conclusions**: summarize the take home messages
QUESTION 1

- In a word (or two or three), what do you think of when you hear “paraneoplastic syndrome”? 
INTRODUCTION
Full disclosure: I am not a PNS expert
As a medical oncologist in Victoria I treat …

- Breast Cancer
- Brain Cancer
- Bowel Cancer (and other GI malignancies)

(My cases come, largely, from this cohort)
Direct vs Indirect Effects of Cancer

- Cancer
  - Mass Effect
    - Organ failure
    - Effects of therapy
  - Immune responses
  - Hormone/cytokine secretion

- Distant Cancer
Paraneoplastic Syndrome (PNS) defined:

Paraneoplastic syndromes are

- symptoms that occur at sites distant from a tumor or its metastasis.
- clinical syndromes involving nonmetastatic systemic effects that accompany malignant disease.
- syndromes that occur when a cancer causes unusual symptoms due to substances (i.e., hormones, antibodies) that circulate in the bloodstream.
Armand Trousseau (1801 – 1867)

- Astute observer
- Celebrated instructor
- Has his own syndrome!
- Public health expert
- Designed surgical instruments
- Politician (post French Revolution)
- Spawned a long line of famous physicians
Armand Trousseau (1801 – 1867)

- Clots and cancer seem to co-exist
- Trousseau’s Syndrome is the existence of multiple superficial clots in various parts of the body over time
- These clots are sometimes found at multiple locations and can occur in uncommon sites
- Most commonly associated cancers were gastric, lung and pancreas

So great, in my opinion, is the semiotic value of phlegmasia in the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the serous cavities.
INTRODUCTION

Armand Trousseau (1801 – 1867)

- Clots and cancer seem to co-exist
- Trousseau’s Syndrome is the existence of multiple superficial clots in various parts of the body over time
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“If I see clots in a patient who is cachectic, they very likely have cancer”
INTRODUCTION

Trousseau developed Trousseau’s Syndrome and diagnosed himself with gastric cancer in 1867.

I told you it was serious…
INTRODUCTION

If you were a member of the “Society of Mutual Autopsy” you could perform autopsies. However, when you passed away, it was then your turn to educate the group.
Following autopsy, Trousseau was diagnosed with pancreatic cancer (not gastric cancer)
INTRODUCTION

Understanding Trousseau’s Syndrome: in prostate cancer

- Prostate cancer cells secrete microvesicles with long chain polyphosphates on their surface
- These microvesicles activate Factor XII
- Activation of Factor XII leads to thrombosis

Local cells → Systemic effect

Blood 2015; 126: 1270-1272.
MECHANISMS
Direct vs Indirect Effects of Cancer

Cancer

Organ failure
Effects of therapy

Mass Effect

Distant Cancer

Hormone/cytokine secretion

Immune responses
“This is Dr. xxxxx of Neurology…”

“We’d like you to see this 63 year old female…”

“She presented a week ago with ‘opsoclonus-myoclonus syndrome’… opsoclonus-myoclonus… ‘Dancing Eye Syndrome’…hello?”

“Our workup revealed a lung lesion and the biopsy was positive for small cell lung cancer”
Unwell
Not herself
Doing strange things

Rapid eye movements
Ataxia
MRI normal

Opsoclonus
Myoclonus Syndrome

Malignancy found in 60% of cases
In adults, SCLC is #1 cause
Rule out infections, toxins, sarcoid...
MY FIRST ONCOLOGY CONSULTATION

How neurology approached this case...

Search for antibodies...

Give steroids a try...

Work up for malignancy
This 62 year old male had a 94 pack-year history of smoking.
The metastatic work up was clear (no lung cancer)

A SIMILAR CASE IN THE LITERATURE…

<table>
<thead>
<tr>
<th>Antibodies Against</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HU</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>CV2</td>
<td>Serum</td>
<td>Positive</td>
</tr>
<tr>
<td>Ma1, Ma2</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>amphiphysin</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>GAD</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>LGI1</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>CASPAR2</td>
<td>Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>NMDAR</td>
<td>CSF</td>
<td>Negative</td>
</tr>
<tr>
<td>CAMPAR</td>
<td>CSF</td>
<td>Negative</td>
</tr>
<tr>
<td>GABABR</td>
<td>CSF</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CV2 is an antigen on oligodendrocytes…

Diagram from Lancet Neurology VOLUME 1, ISSUE 5, P294-305, SEPTEMBER 01, 2002
- He didn’t respond to a pulse of steroids or to intravenous immunoglobulins (IVIG)
- They decide to give him methylprednisolone and cyclophosphamide...full phasers!
## A SIMILAR CASE IN THE LITERATURE…

<table>
<thead>
<tr>
<th>DAYS</th>
<th>Monthly dose (every 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methylprednisolone (1 g/24 h) IV</td>
</tr>
<tr>
<td>2</td>
<td>Cyclophosphamide (50 mg/kg/h) IV</td>
</tr>
<tr>
<td>3</td>
<td>Pantoprazole (1 vial) (40 mg/24 h) IV</td>
</tr>
<tr>
<td>4</td>
<td>Fluid therapy, 0.9% saline solution (2000 cc/24 h): 15 mEq KCl/500 cc saline solution</td>
</tr>
<tr>
<td>5</td>
<td>Clinical and haemodynamic monitoring</td>
</tr>
<tr>
<td></td>
<td>Complementary tests to complete aetiological study</td>
</tr>
</tbody>
</table>

His symptoms immediately resolved!

When they tried to reduce the doses one year into therapy his symptoms recurred, and small cell lung cancer was detected.

Unfortunately he passed away 7 months later.
WHAT HAPPENED HERE?

The Normal Cell

- Cell switched on at appropriate times
- Limited access to genome
- Only appropriate proteins are made

The Cancer Cell

- Cell switched on inappropriately
- Cell starts to read from “forbidden” parts of genome
- The wrong proteins are made
THE IMMUNE SYSTEM ATTACKS THE NORMAL PROTEIN, ON NORMAL CELLS

Diagram from Lancet Neurology VOLUME 1, ISSUE 5, P294-305, SEPTEMBER 01, 2002
Direct vs Indirect Effects of Cancer

- Cancer

  - Mass Effect
    - Organ failure
    - Effects of therapy

- Distant Cancer

  - Immune responses
  - Hormone/cytokine secretion
TUMOUR FEVER

Necrotic cell → Interferon
IL-1
IL-6
IL-10
TNF-α
(inflammatory cytokines)
→ Cancer cell

…C-Reactive Protein, Fever…
35 year old male with giant cell tumour of left femur

Presents 40 years later with left leg pain, swelling, fever of unknown origin

Arthrocentesis, plain film, CT all clear

Surgical debridement (presumed osteomyelitis)
Found tumour cells in sample, plus TNF-α
Gave naproxen and fever resolved
Amputated femur
Fever resolved; no recurrence of fever or tumour
TWO MAIN MECHANISMS

Immune Mediated
- A cancer cell expresses proteins inappropriately
- The immune system identifies the proteins and creates antibodies, etc
- The immune system attacks any cell that expresses that protein, even if they are normal cells

Hormones / Cytokines
- A cancer cell secretes hormones and/or cytokines inappropriately
- These hormones and/or cytokines create a cascade of effects within the body
A small number of cancer cells can start this process

The associated process might be “visible” before the cancer itself is detectable

The PNS might just be the tip of the iceberg

Created by Shizuka Aoki; published in Canadian Geographic 11 April 2017
CASE 1: SALTY SAM
SALTY SAM

- Samantha is a 61 year old female
- She was diagnosed with “curative” breast cancer four years ago and metastatic disease just one year ago (recurrence in bone only)
- Doing well on letrozole (endocrine therapy) and pamidronate (bisphosphonate)
- On 3 month follow up…
Sam was very unwell and her GP, Dr Smarts, brought her in for a full assessment.

The only abnormality found was low sodium at 129.
QUESTION 2

- What is the cause of her low sodium?

- Dehydration
- SIADH due to drugs
- SIADH due to cancer
- SIADH due to stroke
CASE 2: Ms. DIAGNOSIS
Ms. DIAGNOSIS

- Miss Diagnosis is a very busy 54 year old professional female with virtually no medical history.
- She is also a patient of Dr Smarts.
- Suffers from intermittent diarrhea, bloating, dyspepsia, and flushing.
- She has a supportive partner, no kids, and she remains productive despite her complaints.
QUESTION 2:

- What do you think is the cause of these complaints?

- IBS
- Chronic Gum Chewer
- Carcinoid syndrome
- Menopause
- Parasites
SALTY SAM

(BACK TO CASE 1)
Dr. Smarts was concerned about a low sodium measurement of 129 mmol/L.

Dr. Smarts wondered about the etiology of low sodium; was this SIADH?

Dr. Smarts knew that breast cancer with metastases to bone was not likely to cause SIADH; were there metastases in the lungs or brain?

Dr. Smarts began fluid restriction but wanted to hear my thoughts on a metastatic work up.
WE FOUND THE LIKELY CAUSE OF SIADH…
Fluid restriction didn’t work…
Did not feel we needed hypertonic saline
Gave “salt” a try…
SYNDROME OF INAPPROPRIATE ANTI-DIURETIC HORMONE SECRETION

A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Antidiuretic Hormone

William B. Schwartz, M.D., Warren Bennett, M.D., and Sidney Curotto, M.D.

Boston, Massachusetts

and Frederick C. Bayter, M.D.

Baltimore, Maryland

This paper is a report of studies of two patients with bronchogenic carcinoma in whom hyponatremia developed as the result of unexplained failure of renal sodium conservation. The data indicate that sustained inappropriate secretion of antidiuretic hormone was probably responsible for the disorder of sodium metabolism. The physiologic abnormality appears to be analogous to that which can be produced by the continuous administration of pitressin and water to normal subjects.

Case Reports

Case 1: W. A., a sixty-year-old man, complaining of coughing up bright red blood for the previous six weeks, and loss of 15 pounds of weight. On physical examination, he was well-nourished. The blood pressure was 120/70 mm. Hg. There was oedema of the fingers and toes which the patient said had been present all his life. Physical and urinalysis examination was otherwise within normal limits.

Initial roentgen laboratory studies revealed no abnormalities in the hemogram. Urine examination was negative. Intravenous pyelogram revealed normal structure and efficient dye concentration in both kidneys.

X-ray revealed a 4 by 5 cm. ill-defined mass in the region of the right pulmonary artery. A biopsy by bronchoscope demonstrated atypical carcinoma of the right main stem bronchus, and an exploratory thoracotomy revealed an inoperable tumor at the right hilum infiltrating the trachea and aorta. In the postoperative period empyema developed, which was satisfactorily controlled with antibiotics and sterile solution irrigations. Two weeks after operation serum electrophoresis and protein concentrations were measured as a routine procedure. The following values were obtained: sodium, 121 mEq./L.; potassium, 4.6 mEq./L.; chloride, 88 mEq./L.; carbon dioxide content, 24 mEq./L.; calcium, 10.0 mg. per cent; inorganic phosphate, 4.0 mg. per cent; calcium, 2.1 gm. per cent; globulin, 3.7 gm. per cent. The hemoglobin was 9.8 gm. per cent. The patient was given small amounts of normal saline solution and on the following day his serum sodium was 114 mEq./L. and his blood urea nitrogen was 2 mg. per cent. The urine sodium concentration was 75 mEq./L. At this time the physical examination was within normal limits. The blood pressure was 134/86 mm. Hg. Skin turgor and hydration were good. There was no abnormal pigmentation and auxiliary and pubic hair were normal. During the next two days he was given hypotonic sodium chloride, despite which his serum sodium concentration fell to 103 mEq./L. During this time he was asymptomatic. He was then given small doses of DDAVP and very large amounts of supplementary salt. Three days later metabolic studies were begun,

*From the Department of Medicine, Tufts University School of Medicine, and the New England Centre Hospital, Boston, Massachusetts and the Section of Clinical Endocrinology, National Heart Institute, National Institutes of Health, Bethesda, Maryland. Supported in part by grants-in-aid from the National Heart Institute, National Institutes of Health, U. S. Public Health Service and the American Heart Association. Present in abstract, April 26, 1956, American Society for Clinical Investigation [7].

† Established Investigator of the American Heart Association.

‡ Research Fellow, National Institute of Health, U. S. Public Health Service.

§ Chairman, Tufts University School of Medicine, Boston, Massachusetts.
LOTS OF REASONS TO HAVE HYponatremia….
LOTS OF REASONS TO HAVE SIADH....
AMONG CANCER PATIENTS, MALIGNANCY ASSOCIATED SIADH IS WORSE…

AMONG CANCER ASSOCIATED SIADH PATIENTS, THE LOWER THE SODIUM THE WORSE THE PROGNOSIS…

SIADH is underdiagnosed, and poorly understood
Recall your differential diagnoses for hyponatremia, and for SIADH
Find the cause: prognosticate
Correct it, and improve morbidity, and perhaps mortality
CASE 2: Ms. DIAGNOSIS

(BACK TO CASE 2)
Ms. DIAGNOSIS

- Eventually presents to ER with nausea, vomiting, abdominal pain
- CT imaging reveals source of obstruction in small bowel and multiple liver lesions
- Immediately proceeds to surgery for resection of primary tumour in small bowel
- Surgeon says it “looks like a carcinoid”
Carcinoid means “cancer-like”
Neuroendocrine tumour are real cancers
30-40% of these tumours secrete serotonin and create a PNS
The accompanying PNS is still called “carcinoid syndrome”
Ms. DIAGNOSIS

- The carcinoid syndrome continued after the resection of the primary tumour
- Somatostatin analogs gave Ms. Diagnosis her life back

From Wikipedia, carcinoid syndrome
Ms. DIAGNOSIS

- At follow up appointments we see the symptoms re-appear when her monthly injections approach
- At annual imaging we see a little bit of growth each year
- Life expectancy is ~15 years...
Recall the nature of this disease
Delay in diagnosis is common
Somatostatin analog therapy helps
When you hear hoofbeats…
CONCLUSIONS

A word from the oncology trenches…

- We see the cancer first, and then see the PNS
- Having a PNS is a worrisome sign
- We usually treat the underlying cancer to treat the PNS
Key Points

- Fascinating syndromes, limitless variability
- Our understanding is limited by the “unknown unknowns”
INTRODUCTION

- PNS are all around us
- You and I see them
- Is this the cancer or a PNS? (what's the difference?)

Steve Jobs
1955-2011
CONCLUSION

- Thanks so much!