The Curious Case of Synchronous Colon Adenocarcinoma and CLL

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- Mr CC (27/04/1977) 42 year old male.
- Presented to the PAH ED in July 2019
  - 18/12 history of episodic cramping abdominal pain.
  - Intermittent episodes of diarrhoea and dark bowel motions.
  - Increasingly debilitating fatigue.
  - Minimal findings on examination other than small but palpable pre auricular and occipital lymph nodes.
  - Routine bloods revealed.
    - LDH 301; WCC 41.6 – Lymphocytes 35; Normal HB and platelets.
    - Negative haemolysis and Coombes test

- Background history was largely unremarkable.
  - Lives locally
  - Worked as a journalist with a community radio station and is a singer with Opera Queensland.
  - Ex smoker having ceased 10 years ago.
  - No recreational or IV drug use.
  - Very keen cyclists however this had been restricted over the previous 3-4 months due to his fatigue.
  - Significant family history of malignancy.
    - Mother had passed away from a BRCA + breast cancer in her 30s.

- In view of the lymphocytosis, a number of investigations were instigated including flow cytometry and FISH.
  - Diagnosis of B cell CLL with 17p deletion, 13q deletion and heterozygous p53 deletion.
  - In view of his GIT symptoms, a colonoscopy was ordered to determine possible colonic CLL involvement or a secondary pathology.
  - At clinic review (Dr Paula Marlton) it was noted that Mr CC was displaying clinically apparent progressive lymphadenopathy along with worsening constitutive symptoms.

- Staging CT chest abdominal and pelvis was performed.
- Enlarged bilateral axillary lymph nodes.
- Enlarged retroperitoneal, iliac chain, pelvic side wall and inguinal lymph nodes radiologically consistent with a lymphoproliferative disorder.
- Mass in the transverse colon with no evidence of metastatic visceral disease seen elsewhere.

- At colonoscopy (11/10/19): an ulcerated partially obstructing mass in the proximal transverse colon.
- Pre-operative CEA was 5.0.
- Laparoscopic Extended Right Hemicolectomy.
  - Transverse colon: 29mm mod-diff adenocarcinoma extending to the serosal surface; LVI/PNI+; MSI stable (pT4a)
  - Caecum: 48mm mod-diff adenocarcinoma invading through the muscularis propria into fat and extending to the ileocaecal valve; LVI/PNI+; MSI stable (pT4a)
  - 7/46 resected lymph nodes +; 1 apical LN +CLL
  - Staged as Stage 3C colonic adenocarcinoma.

- Discussed at the Colorectal MDT and subsequently at a joint meeting of the medical oncologists along with Dr Marlton.
- Ordered WES and germline testing of his CLL and Colon cancer.
- Commenced a course of adjuvant Folfox Chemotherapy.
- Combination of 5-FU 48 hour infusion, along with bolus 5-FU and Leucovorin and oxaliplatin; currently approaching the mid point of 6 months of chemotherapy
  - Overall doing well although has required a DR of the oxaliplatin due to peripheral neuropathy.
  - Restaging CT scans have shown interval improvement (albeit small) in the cervical and axillary adenopathy with no evidence of recurrent or metastatic colorectal cancer.
  - Yet to commence treatment of his CLL.

Molecular Profile Somatic

Tumour Mutational Burden:	4.4 Mutations/Mbp
Tumour Purity Estimate:	50-70%

Somatic Mutations Summary

There were 2 reportable variants found in this sample.

Gene	Mutation	Consequence	Variant Allele Frequency
NRAS	NP_002515.1:p.Gln61Arg	missense_variant	31.0%
PTEN	NP_001291646.2:p.Arg247Ter	stop_gained	45.0%

Somatic CNV Summary

There were 3 reportable CNVs found in this sample.

Gene	CNV Type	Copy Number	Start	Stop	Length	Whole/Partial
PTEN	LOSS	1	75,671,312	106,139,897	30,468,586	Whole
TP53	LOSS	1	7,094,025	8,224,311	1,130,287	Whole
SMAD4	LOSS	1	43,795,845	61,030,101	17,234,257	Whole

NRAS (level A for colon cancer)
PTEN (level B for colon cancer)

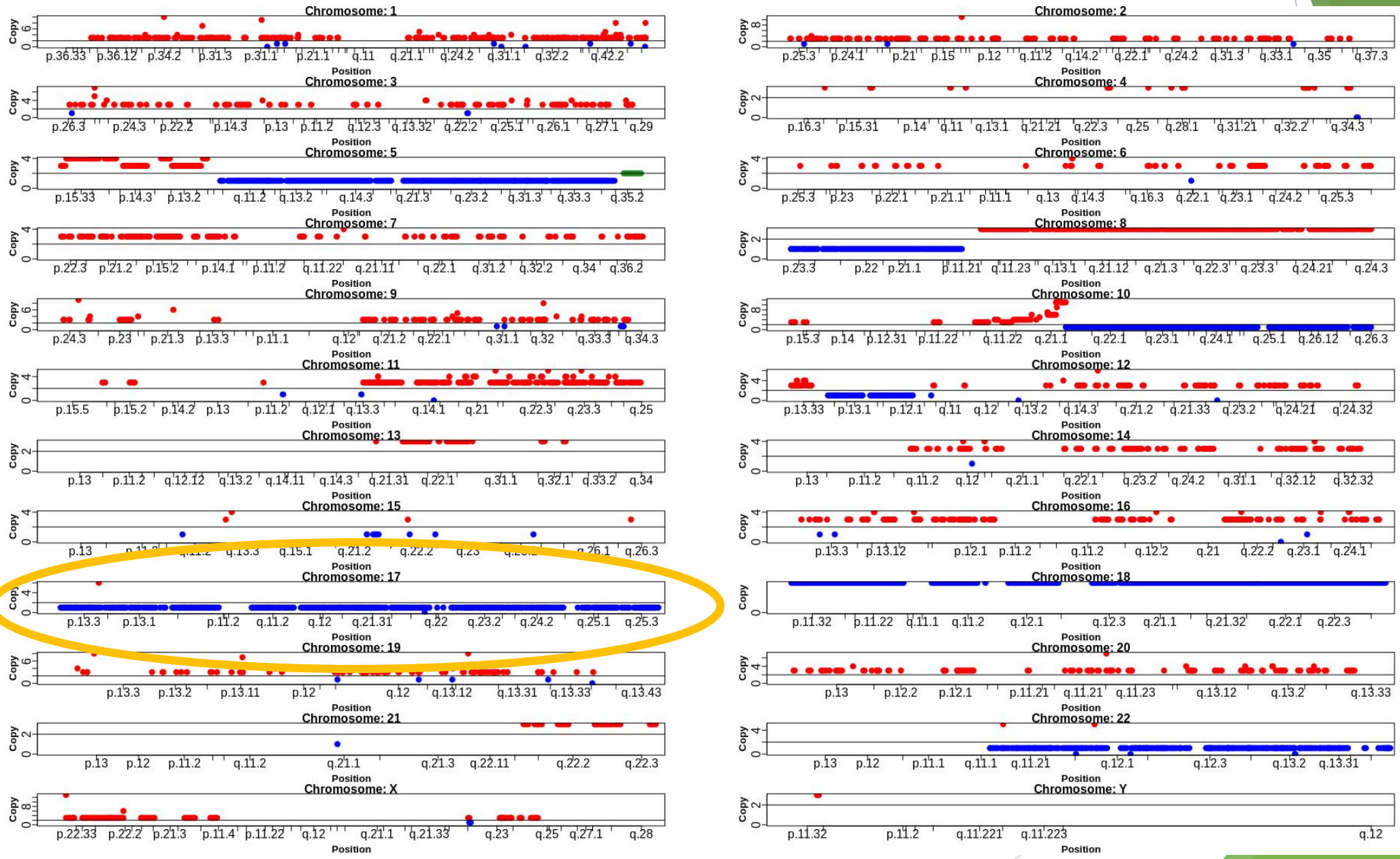
- NCCN panel strongly recommends KRAS and NRAS testing with stage IV

"Patients with known KRAS or NRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified."

- FOLFIRI plus bevacizumabdo better (6.1 vs 12.2 months; P=.004).
- Non functional PTEN also associated with resistance to anti-EGFR. *

* Therlildren et al The predictive value of KRAS, NRAS,PIK3CA and PTEN in anti-EGFR treatment in metastatic colon cancer Acta Oncol 2015

Somatic Colon Cancer:TP53 loss as chr17 deletion:



Germline (preliminary)

TP53

Gene	TP53 (stop_gained, VAF = 44.6% AD = 379,306)
HGVSg	NC_000017.10:g.7578212G>A
HGVSc	NM_000546.5:c.637C>T
HGVSp	NP_000537.3:p.Arg213Ter
Heterozygosity	0/1 (Heterzygous)
CLINVAR	Level 5 - Pathogenic single nucleotide variant (https://www.ncbi.nlm.nih.gov/clinvar/variation/43590/)

CLINVAR Interpreted condition: Li-Fraumeni syndrome, familial 1; Hereditary cancer-predisposing syndrome ACMG/AMP 2015 Criteria Assigned: PVS1, PM2, PP5. ClinVar contains an entry for this variant: rs397516436.

Referral to Genetic Health Queensland is recommended for conformational testing.

Described as Pathogenic by Invitae, GeneDx, Ambury Genetics

Li-Fraumeni Syndrome

- Lifetime cancer risk 70% men, 100% wemon
- Includes early onset colorectal cancer.
- Screening 2-5 years starting at age 25
- Malignant transformation seen in small polyps (3mm)

- NCCN also suggests

- Perform annual whole body MRI (rapid non-contrast exams per ACRIN model).
- The brain may be examined as part of whole body MRI or as a separate exam.

Discussion

- Radiation
- KRAS/NRAS status as a plan for the treatment continuum