**Early onset of head and neck squamous-cell carcinoma and fatal toxicity with concurrent chemoradiotherapy in a patient compound heterozygote for FANCA gene.**

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Case report.

We report on a 43-year old man without smoking history who was diagnosed with locally advanced cT2a N2c M0, squamous-cell carcinoma of the left pyriform sinus.

In his medical history he reported bilateral congenital clubfeet treated surgically during infancy, idiopathic growth-hormone deficiency supplemented between the age of 14 and 17 (size increased from 131 cm to 160 cm) and chronic, unexplained, liver tests alteration (alkaline phosphatase < 2.5 x ULN, gamma-glutamyltransferase < 2.5 x ULN).

He was scheduled for concurrent radio-chemotherapy using weekly 40 mg/m² cisplatin but only 2 doses could be given (total cisplatin dose received = 80 mg/m²). Radiotherapy was also interrupted after a dose of 20 Gy had been delivered.

Ten days after treatment start he developed severe toxicities including grade 4 stomatitis and grade 3 diarrhoea. He had to be hospitalized and a feeding tube was required. By day 14, he had developed profound pancytopenia (grade 4 neutropenia, grade 4 thrombocytopenia, grade 4 anaemia) complicated with fever and ileitis with ileus. Necrotizing enterocolitis was diagnosed. He was given large spectrum antibiotics and granulocyte-colony stimulating growth factor (G-CSF) with no success.

A bone-marrow trephine biopsy revealed a complete atrophy with no regeneration signs.

His clinical condition declined and he was admitted to the ICU on day 44. ARDS due to alveolar haemorrhage, severe hyperbilirubinemia and end-stage kidney failure occurred successively despite neutrophils recovery with G-CSF. In spite of maximal care including daily RBC or platelets transfusions, multiple antibiotics and artificial ventilation he deceased on day 74 due to multi-organ failure without platelets, gastro-intestinal and mouth toxicities recovery.

Because of such an unexpected early toxicity profile we suspected some genetic susceptibility to chemotherapy and/or radiotherapy toxicity. A family inquiry revealed that the Italian ascendant parents were consanguineous (first cousins). The patient’s only brother and a maternal first cousin also had a clubfoot; the patient’s only sister is healthy. A comprehensive genetic analysis was undertaken on stored DNA from a previous testing and focusing on Fanconi anaemia (FA) genes. This analysis revealed mutations in FA complementation group A (FANCA) and that our patient was a compound heterozygote for the mutations: FANCA c.4198C>T (p.(Arg1400Cys)) and a deletion spanning exon 22-43: FANCA c.(1900+1\_1901-1)\_(\*1050\_?)del. No mutation was diagnosed in the other FANC genes.

The chromosome breakage test in which lymphocytes are exposed to mitomycine C or diepoxybutane (DEB) was not feasible because of deep leukopenia.

Discussion:

FA is a complex clinical condition which is secondary to mutations occurring in any of at least 22 genes [1]. The diagnosis is most commonly made during childhood but depending on the clinical expression it can be made in adulthood as happened with our patient. FANCA mutations account for 2/3 of FA mutations [2] and most FANCA families harbour a distinct set of mutations [1]. Before cancer diagnosis and treatment toxicity occurred nobody had suspected FA despite small signs such as short stature and small hands. In particular no haematological abnormality was observed before treatment started although most patients with FA exhibit early anaemia frequently before the age of 10. Furthermore, parents’ consanguinity was not known even from the paediatrician who prescribed growth hormone when the patient was diagnosed with idiopathic growth hormone deficiency as a teenager. At that time a normal karyotype 46, XY was obtained but a spermogram revealed azoospermia.

The limited clinical signs in our patient may stem from its compound heterozygote status although genotype to phenotype correlations are heterogeneous to some extend as described previously [3].

Unfortunately we could not obtain DNA from our patient’s parents, despite being first cousins our patient was not homozygous for a single mutation but instead a compound heterozygote suggesting that each parent was harbouring a different FANCA mutation or that the deletion appeared *de novo*. The patient’s only brother was shown to carry FANCA c.4198C>T (p.(Arg1400Cys)) while his sister had no mutation.

Increased early incidence of head and neck squamous-cell carcinoma (HNSCC) has been reported among patients with FA [4,5] with poor tolerance to radiotherapy and chemotherapy. HNSCC is a potential initial clinical manifestation of FA with fatal treatment-induced complication reported [6]. It is noticeable that the clinical course we report is superimposable to the one described by Tan et al with locally advanced pyriform sinus squamous cell carcinoma occurring early in age without classical risk factors (tobacco use and/or HPV infection the latter for oropharyngeal cancer only). Marrow toxicity to cisplatin is dose-dependent and commonly reaches grade 3 or higher with cumulative dose > 100 mg/m² but is rapidly reversible [7].

FANCA silencing has been shown in vitro to increase susceptibility to radiotherapy of HNSCC cell lines with 16q23-24 (where FANCA is located) amplification [8]. Although cisplatin sensibility seemed higher in FANC-C and FANC-CD2 cell lines as compared to FANCA [9], patients harbouring biallelic FANCA mutations were also reported to exhibit higher sensibility to cisplatin [6] while a patient who harboured a mono-allelic germline FANCA variant (S1088F) with additional somatic hemizygous copy-number loss of FANCA in his small-cell neuroendocrine metastatic prostate cancer cells experienced a remarkable response to cisplatin without excessive toxicity [10]. This observation is supported by the demonstration that the FA/BRCA pathway is the predominant one for cisplatin response in HNSCC cells [11].

This case-report draws attention to unrecognized FA disease and especially FANCA disease that can lead to fatality when exposed to chemotherapy. Attention should be paid to patients developing early HNSCC without previous exposition to known risk factors and anamnestic information suggesting FA such as limb congenital abnormalities, growth deficiency with short stature (with or without growth-hormone substitution) and family history. Those patients should receive upfront genetic testing or undergo DNA breakage test with DEB, a potentially faster alternative to genetic testing. Chemotherapy should be avoided and surgical treatment should be preferred. If not feasible radiotherapy alone or, maybe, potentiated by cetuximab which is not expected to generate DNA-crosslinks per seand seems to be safe in that setting providing increased attention is paid to toxicity [12,13].

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Figure 1: Patients’s family tree