ONCOLOGY

Elective report:

Name: SJC PALLETT

Title: Clinical research: Primary signet ring cell carcinoma of the rectum and colon

Location: Royal London Hospital, Whitechapel, UK

Aims:

1. Gain greater insight to clinical surgical based research
2. Gain greater insight to the presentation, diagnosis and treatment of rare and aggressive forms of colon and rectal cancers
3. Improve skills for academic search techniques, retrieving pathology data and compiling databases of relevant data sets.
4. Better understand the process of designing clinical research questions, gaining ethical approval, identifying appropriate patients and carrying out the experiments.

Introduction:

Signet ring cell carcinoma (SCC) of the colon is a rare condition; it has a tendency to present late, in comparatively young patients and with an aggressive, infiltrative pattern. It has long been thought that the mucinous colorectal adenocarcinomas carry with them a worse prognosis than non-mucinous carcinomas but there remains controversy over, firstly, whether SCC as a subtype of mucinous adenocarcinomas acts as an additional independent poor prognostic factor and secondly whether this can be accounted for by a separate molecular mechanism. Following a review of the current literature comparing SSC outcomes with both mucinous and non-mucinous adenocarcinomas, the aim is to identify appropriate patients within Barts Health and design a molecular screen that looks at the expression of a number of suspect genes that may be associated with how SSC of the colon presents in such an aggressive fashion.

Mutations in cytokeratins, BRAF, K-RAS and MSH instability have all been associated with primary SSC and investigated in reports that are generally on a small numbers of cases. Beyond these previously suspected molecular pathways we will take the opportunity to look at telomere length as a prognostic factor in subtypes of colorectal cancers and consider the microsatellite instability route but from the angle of DNA methylation profiles.

A number of primary signet ring cell adenocarcinomas in the younger patients occur on a background of chronic inflammation caused by inflammatory bowel disease.Nox and Duox genes are highly expressed in the gastrointestinal tract and although they have an unclear role, they are connected to the production of greater amounts of reactive oxygen species and may provide better understanding into inflammation-driven carcinogenesis[53].It would be interesting to view these cases to look at the expression of inflammatory genes in the progression of primary mucinous signet ring cell adenocarcinomas in the lower GI tract.

Background of primary SCC literature:

Colorectal cancer is a considerable health burden. Whilst reported to be remaining stable or decreasing in the elderly, it is increasing in younger patients[30]. SCC is known to be a disease that

occurs more commonly in the young[11]. It should be considered that HNPPC occurs in a high proportions of young patients (<40 years) in a similar fashion and therefore hereditary genetic factors should also be considered in the case of SCC development in the young.

Survival rates are worse in cases of SCC when compared with non-mucinous adenocarcinomas as well as when compared with other mucinous subtypes. Despite microsatellite instability seemingly conferring a prognostic benefit for colorectal adenocarcinoma this appears to be lost due to SCC presenting late, at a higher grade and with an aggressive, infiltrative nature that shows widespread invasion of the submucosa. Patients with SCC have poorer overall outcomes than mucinous and nonmucinous adenocarcinomas[10].

Signet ring cell histology is an independent prognostic factor for a colorectal cancer diagnosis[11,16]. The association between a worse clinical outcome with and a SSC histology diagnosis remains unclear. This is largely due to the fact that it is such a rare condition; evidence is largely provided by small case studies, the larger studies are limited by being retrospective in nature. It is difficult to answer several arising questions, such as the role and significance of microsatellite instability as this data has often not been collected in the past. More large-scale studies are required in order to confirm that which is already known regarding epidemiology and to offer insight into the molecular nature of SCC to see if it has a unique pathogenesis within colorectal tumours.

Many molecular pathways have been suggested to play a key role in the pathogenesis of SCC colon carcinoma; alongside the wide range of ages seen at presentation it may be that it is not a single pathway responsible for the characteristics seen. The variety of colon related pathologies that it is linked to suggests this may be the case.

Further case reports may continue to add weight, or confusion, to the defining aspects of SCC as well as to the question of whether SCC should be treated as a separate entity in terms of a clinical or a molecular approach. The rarity of the condition provides significant problems to progress; we are still asking the same broad questions as a decade ago. I feel molecular studies seem to offer the best chance of learning more about this condition; it would be helpful for future large scale studies, from varying population sets, to analyse molecular changes in SCC as part of their study design in order to better understand the development and treatment of signet ring cell adenocarcinoma of the colon.

Elective experience:

This work has proven to be far more difficult to advance than previously imagined. Despite having done similar work in the past I did not fully appreciate the difficulty in bringing together clinicians and scientists from various fields, despite a combined interest, to keep advancing the tasks at hand. From this I feel I need to bear two things in mind for the future. Firstly, a more realistic time frame that is enforced by a more rigid timetable agreed upon at the outset. Secondly, to be more active in chasing opportunities to advance the work instead of always waiting for another's greatest convenience.

Through viewing the work load of my seniors, and the great difficulty through which academic and clinical work is balanced I feel it is important to start to work out these problems now and generate better work habits, in order to not become disheartened further down the line.

Through this work I have come to better understand the role, balance of work and see some of the difficulties that face an academic clinician. In saying this, it has further strengthened my desire to pursue an academic surgical career.

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