Spontaneous regression of tumours and their metastases – a comment on whether it is really immunologically driven

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Surrounded by talented informaticians, I remain nonetheless old school in my philosophy of biomedical discovery. I believe that medical science is mainly detective work, and that analysing individual human cases remains an important source of insights [1].

That this viewpoint has become largely passé in many circles was brought home to me when I asked a leading clinical researcher his opinion of cases of spontaneous regressions of metastatic malignant melanoma [2]. He replied simply "I am sceptical because these cases occur so rarely as to be anecdotal" – a Catch-22 situation!

In order to be methodologically rigorous, we must throw out of court – due to a technicality – the only clues we have to the factors that lead to rapid elimination of metastatic deposits. But it is instructive that, despite an apparently vast knowledge gap, the default explanation is almost always immunological, i.e. unexpected regressions must be due to "anti-tumour immunity." [3,4]

I started doubting this explanation while a post-doctoral fellow in the T cell tolerance section of the Laboratory of Cellular and Molecular Immunology at NIH, although I had myself used it to explain inverse associations between cancer and inflammatory diseases [5-21], as well as relatively improved survival in familial cancers in the face of multiple primaries [22]. Clinical geneticist, Henry Lynch [23], described a brother and sister who showed complete spontaneous regressions of metastatic malignant melanoma, and postulated co-inheritance of heightened anti-tumour immunity compensatory for extreme tumour propensity.

But thinking back on the roots of current thinking about immunity against cancer, in the light of current knowledge of its pathogenesis [24], makes one wonder if something important was not missed at the very beginning of the enterprise. Cancer immunotherapy has its conceptual origin in late 19th and early 20th century cases of spontaneous regression of sarcomas, which occurred during local infections like erysipelas, and which led to Coley's mixed toxins thought to boost anti-tumour immunity along with anti-bacterial immunity [25,26].

But in the years since Coley's work, a single clear case of an immune response eliminating a human solid tumour has yet to be adduced. Indeed, immunotherapies that are most carefully targeted to antigens of the tumour, and which would purportedly lead to lymphocyte-mediated destruction of tumours, are the least likely to extend overall survival [27,28]. Ironically, immunotherapy works best when something goes wrong, particularly when an unintended autoimmune process is induced in tissues often far from the tumour and its metastases [29-33].

So what is similar about the sarcoma/erysipelas and the melanoma/autoimmunity cases? Unlike Coley and his early successors, we find ourselves squarely on the horns of the central paradox of immuno-oncology. Inflammatory cells are not universally involved with suppression of the growth of cancer; in fact, data suggesting that inflammatory cells foster cancer are far more direct and abundant than the notion that they fight it, particularly if clinical cancer is taken as the gold standard [34-36]. An evidence-based approach to the question just posed suggests one should look more carefully at how many and what kind of inflammatory cells have been feeding the cancer in each case rather than whether immunity was induced.

Why has no one asked – is it possible that the erysipelas infection or the autoimmune process somehow out-competes the tumour for sustaining monocytes and/or other inflammatory cells? It is now known that, during fever, monocytes can apoptose due to glutamine depletion [37,38], and this restriction on monocyte numbers may heighten competition for such inflammatory cells between tumours and tissues damaged by infection [39]. This idea may provide a new explanation for the original regressions noted by Coley.

Although we tend to think of the bone marrow as unlimited in its capacity to produce monocytes [40], at my request, University of Pittsburgh biomathematician Bard Ermentrout derived simultaneous equations describing the situation encountered in a patient undergoing immunotherapy who sustains, say, intense inflammation of the gastrointestinal tract as an unintended side effect. In fact, these equations show that when the GI lesions are weighted sufficiently with inflammatory cell infiltration, they could outstrip the capacity of the marrow to supply enough inflammatory cells to the tumour and its metastases to keep them actively growing.

Undoubtedly, the overall "poising" of the patient's marrow capacity due to past radiation or chemotherapy and other factors would tend to determine whether too few inflammatory cells might be available for metastatic growth. This might explain why we remain unable to predict which patients will benefit from any particular immunotherapy or who experience miraculous disappearance of their metastases following simple palliative radiotherapy of a single deposit.

At one of Steven Rosenberg's presentations at NIH about tumour infiltrating lymphocyte immunotherapy

(which has also been shown most effective when serious autoimmune "side effects" occur) [31], one sensed his mixed frustration and excitement when he said "Results of this treatment are usually not dramatic, but when it works, it is as if a fire has been lit." The variability in response to immunotherapy is usually construed as due to variability in the remaining immune competence in patients with advanced cancer [41].

But others have noted that the rarity of complete clinical responses to therapy occurs, not just in immunotherapy, but with chemotherapy, radiation or other treatment modalities [42]. Such remarkable responses as those that occur "spontaneously" are almost always attributed to anti-tumour immunity. It is difficult to conceive how complete responses achieved with such a variety of treatment types would be due to anti-tumour immunity per se, although it is true that most treatments do damage tissue to some extent, and therefore induce cellular inflammation.

This raises the question – is it possible that both complete responses to cancer therapy and spontaneous regressions occur through a mechanism that is not entirely immunological in the usual sense? For instance, is it possible that damaged tissues occurring at some distance from most tumour sites draw in so many inflammatory cells that there are not enough marrow precursors left to supply metastatic deposits with the Myeloid Derived Suppressor Cells (MDSC) thought to prevent T cell-mediated attack on the tumours? The very dramatic case of regression of all metastatic lesions following radiotherapy of a single lesion reported by Postow is consistent with this idea [4]. Although these authors highlight immunological correlates of spontaneous regressions, the most pronounced and temporally direct effect of the radiotherapy is on blood monocytes. In their Figure 3 B and C, "bad" HLA-DRlow MDSC-like monocyte numbers plummet immediately following the radiation, while "good" HLA-DRhigh acute inflammatory monocytes sky-rocket. Even more intriguingly, the relative numbers of those 2 monocyte subsets at time-points prior to the radiation are reciprocal at every measurement – so consistently as to create an almost perfect inverted image of one another!

It is apparent that, along with sophisticated analyses of genetic signatures and other bioinformatic methods, creative discovery of new explanations for the origin of spontaneous regression of metastatic disease is still very much needed. A more formal presentation of the idea of monocyte competition will be published in *Cancer Hypotheses.*

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