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Can Translational Medicine Exploit the Reported "Metastatic Inefficiency" of Lung Cancer Spreading to the Liver?

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Abstract

In the early 1950s, 2 scientists considered the making of progress in cancer research. One of them was Arnott, a Harveian Orator, who promoted the view that, if the metastatic pattern appears to be anomalous, it is a pointer to the direction to take in remedial researching. Another giant was Professor Cameron, who delivered a Memorial Lecture on the liver which is now enmeshed in the anomaly viewed as "metastatic inefficiency." As he posited, hypotheses should be formulated to explain such matters even if the outcome seems hopeless. As regards the liver itself, I had illustrated the anomalous patterns and offered an explanation based on the spatial distribution of its discrete secondary deposits. This time, the emphasis is on careful case reports because they graphically confirm the formulated theoretical concepts. As a follow-up, the effective role of the newly named "Erythrocyte Associated Necrosis Factor" (EANF) has been entertained. In all probability, if adequate searchlight is beamed on EANF through the well funded field of translational medicine, breakthroughs ought to arise as regards target therapy. Moreover, this could conduce to cancer cure sooner than later.

Keywords: Cancer; Metastatic inefficiency; Translational medicine

Introduction

Ongoing researches have been carried out fruitfully concerning the liver, especially lung cancer metastasizing to it. Among them, the most attractive were the reports by Leonard Weiss [1,2]. Incidentally, he had privately invited me to contribute the Introductory Chapter in his joint monograph on metastasis [3]. In fact, as he had postulated, the liver is singularly the organ that has multipotent chances for being attacked. And yet, the numerous invading cancer cells easily slip through on account of the "metastatic inefficiency" that has been presumed to be at work! Consequently, explanatory researches had to be undertaken personally. However, in what directions should such researches go?

Method

My work was carried out at the Pathology Department of the Glasgow Western Infirmary, whose historical status was that of being second to none in Britain [4,5]. It included the proposition of a mono-block formalin-fixation method for studying the spread of lung cancer [5]. This simplified the tracing of the footsteps of cancer cells. In particular, on slicing the liver horizontally, striking panoramic colonization patterns became manifest.

Results

Out of the 100 cases personally necropsied, 51 revealed hepatic secondaries. Four classes were recognized topographically. Moreover, individual illustrative cases were selected also as follows:

Lateral class

26 cases, i.e., approximately half of those with secondary deposits, showed a tendency toward lateral clustering. In such cases, the secondaries preponderated in or were confined to one lateral (right or left) lobe. An example suffices thus:

Case B 3366: Whitish tumor tissue presents subcapsularly over extensive areas of the right lobe. On section, the parenchyma is almost non-existent on the right side for a 20 cm diameter neoplastic mass occupies it. Smaller rounded deposits are present in this lobe but none are found on the left side.

Proximal class

13 cases, or a quarter of those with hepatic invasion, manifested proximal clustering. The nodules were confined to the dome or predominated in the cephalic parts of the organ, clearly diminishing in number and size toward the caudal parts as follows:

Case B 2947: The liver is enlarged and contains multiple metastases. On the surface, they appear to be distributed centrifugally in both lobes. On section, it is remarkable how most of the metastatic nodules are packed in the upper part of this organ, the nodules becoming fewer and smaller toward the inferior border.

Medial class

There were 5 cases with medial clustering. In them, the liver appeared to be selectively attacked in its mid-portion:

Case B 2912: The liver shows metastases, about a dozen in number, limited mostly to the middle portion and measuring up to 1 cm across.

General class

The remaining 7 cases showed no clustering. Here, generalized involvement occurred, no particular area bearing the brunt of the invasion:

Case B 3478: The liver is impressively peppered with metastatic nodules of tumor in all areas. The nodules do not vary greatly in size and do not abound in any particular area. By etymological derivation, metastasis signifies that phenomenon of malignant growth which is characterized by change in position [6-8]. Accordingly, it should be helpful to cultivate techniques which can highlight important positional relationships. In particular, such maneuvers should be guided with reasoned examples such as the two published during the early 1950s. Firstly, in a Harveian Oration, Arnott [9] declared that, when an anomaly appears, it should be investigated always to the full because it is likely to lead to interpretative discovery. Secondly, Professor Cameron [10] took time to illuminate carefully during a Memorial Lecture on the liver itself as follows: "Ideas must be sought after and cultivated. We must not be afraid to attempt the impossible, no device or technique that holds out the faintest hope of discovery can be put aside.

Discussion

Undoubtedly, the presumed role of the hepatic artery in distributing tumor to the liver has long been recognized to be anomalous [1,2]. Therefore, what should be done to solve this problem? In this context, three of the four above demonstrated classes are of insightful interest.

In sum, metastasis of the proximal class is particularly intriguing. Certainly, it is difficult to see how the hepatic artery can distribute tumor cells preferentially to the upper parts of the liver. On the other hand, since these upper parts have lymphatic connexions with the mediastinum [11], it is the lymphogenous mode of spread that makes this pattern to be meaningful. As was argued elsewhere, [6] this conclusion probably applies also to the metastasis of the lateral class. Coming to the medial class, the known position occupied by the mid-portion of the liver, as regards its lymphatic drainage [12], accords well with the conclusion that this picture is also in keeping with lymph-borne invasion.

There remains the general class. It is unlikely that lymph-borne invasion can account for such cases. Contrariwise, the presence of evenly distributed colonies is compatible with artery-borne dissemination. Although Robbins [13] regarded those with evenly distributed nodules as "typical" cases, my figures suggest that these are relatively uncommon. Indeed, the ratio of the general class to the other three classes is 7 to 44, i.e., 1: 6. Perhaps this ratio gives some idea of the relative contributions of the arterial and lymphatic systems in terms of traceable dissemination routes from the lung cancer itself to the liver. If this ratio is anywhere near being correct and if other workers substantiate this classification proper, it will mean that the label of "metastatic inefficiency" should be abandoned. Rather, the emphasis should be laid on this organ being, in fact, rich in lymphatic connexions!

In other words, research should be directed in terms of the lymphatics as a whole. Indeed, that which stands out is the thoracic duct itself. Its most significant features are the panoramic appearances of lung cancer cells being transported therein at the moment of death [14]. This was achieved by serendipitously using the Swiss-roll method; this was to the extent of manipulating this duct so compactly that it could be observed on a single microscope slide! This contrasts sharply with the usual tedious tackling of its cross sections [15]. With the slide being made handy, necrosis of cancer cells more or less so foisted itself as to be observed panoramically. In particular, this strictly manifested when cancer cells were commingled with red cells. Therefore, it was hypothesized that a hitherto hidden Factor was manifestly at work smoothly. It was personally named as the "Erythrocyte Associated Necrosis Factor" (EANF) [16].

EANF is noteworthy. Essentially, the intrinsic fate of living cancer cells is naturally exhibited in this peculiar conduit. Thus, as a matter of fact, when 27 lung cancer autopsies were performed from 1818 to 1897, they showed a striking anomaly, namely, that the usually vicious lung cancer cells scarcely crossed the midline! [17] What does this exhibit? Indeed, what looks as an anomaly is fully explained on two grounds, (1) EANF is a signal element based expressly on lung tissue and (2) it is a part of the bodily fighting system. Hence, its efficacy must be at its best in the contralataral soil! In sum, the surprising fact of few or no invading cells surviving across the midline is not only to be expected but also what must happen necessarily.

Incidentally, the scenario of little or no attack of that lung was painted succinctly by Nora Schuster [18]. Note how her phrases rang out in wonderment as far back as 1929 thus:

"I do not know which is the more extraordinary: the way in which paired organs like the suprarenals may be the only organs in the body containing metastatic tumour, or the way in which a large fungating tumour of the lung infecting every other organ of the body should leave the opposite lung completely free from direct or indirect spread."

It is to be noted that Schuster's dejection concerning the selective colonization of both adrenals brings to mind the personally observed formation of "new lymph vessels" between the lung and the centrifugally attacked abdominal lymph nodes [19]. This phenomenon, which has now been designated as "lymphangiogenesis," explains the hitherto puzzling adrenal selectivity [20].

As I see it, human lymph borne patterns are to be studied more carefully henceforth. In particular, my personal recognition of the necrosis of cancer cells in the thoracic duct's microenvironment as being associated with the "Erythrocyte Associated Necrosis Factor" (EANF), should be subjected to recondite researches worldwide [21].

To recall, the former technique of thoracic duct cannulation has had its day [22]. Nowadays, the new technique of intravital videomicroscopy has appeared [23]. Therefore, let it be used in consenting patients to retrieve that necrotic pabulum with which to replicate the EANF in the translational laboratories [24].

Furthermore, lung cancer alone should not be the lock whose key must be invented. It seems to me, as I have suggested elsewhere [25] that the pancreas, should be investigated. I did something about this in the city where I trained [26]. A historical point is that it is a subject that I am acquainted with in terms of EANF [27].

Conclusion

In all probability, well-funded translational medicine laboratories should be poised to go far with the funding now at hand [28]. In conclusion, therefore, let these be achieved with the retrieved pabulum obtained from consenting patients' thoracic duct's microenvironment. Surely, the dawning of breakthroughs could translate to target therapy and conduce to cancer cure sooner than later [29,30].

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