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*CLINICAL CASE*

# Paget's "seed and soil" hypothesis revisited

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## Summary

*Paget's "seed and soil" hypothesis emphasises the importance of the interaction between the tumour cell and its environment in order for metastasis to occur. An unusual case of metastatic renal carcinoma is described with review of the literature surrounding the "seed and soil" hypothesis.*

**Key words:** breast metastasis, seed and soil

## Case presentation

A 56-year-old woman undergoing routine screening mammography in January 1999, was found to have an impalpable solitary opacity in the lower inner quadrant of the right breast. Ultrasound demonstrated a 19 mm diameter solid lesion. Core biopsy confirmed an adenocarcinoma composed predominantly of large cells with abundant granular and clear cytoplasm arranged in trabeculae. The appearance was suggestive of renal cell origin.

Further history and abdominal examination did not reveal any additional symptoms or signs. A renal ultrasound showed a 7 cm heterogeneous mass arising from the left kidney. Staging investigations (computerised tomography and bone scan) confirmed the renal mass with a solitary breast metastasis, but no evidence of any other metastatic disease. The patient underwent simultaneous left nephrectomy and wire-guided wide local excision of right breast. Histology of the primary tumour confirmed a clear cell carcinoma G2, pT4 N0 M1. The breast lesion was confirmed as metastatic clear cell carcinoma that on histology had been excised with a good radial margin (>5 mm).

In November 2001 repeat mammography revealed a lesion in the contralateral (left) breast. Core biopsy was again suggestive of metastatic renal cell carcinoma. A further CT revealed no signs of local recurrence or metastatic disease. The patient underwent a wire-guided left wide local excision and remains well on follow-up.

## Metastasis to the breast

Metastatic lesions in the breast are rare, accounting for approximately 2% of all breast malignancies. The commonest sources are the contralateral breast, lymphoreticular tumours, melanoma and bronchogenic carcinoma [1]. Renal cell carcinoma contributes to approximately 3% of metastases to the breast, and is usually a sign of advanced disease [2].

Literature review has demonstrated a single reported case of bilateral breast metastases from a previously occult primary renal cell carcinoma in an adult [3], and one case of bilateral breast metastases in a child who had a previous nephrectomy for renal car-

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cinoma [4]. In both instances the breast lesions were synchronous.

## "Seed and Soil" hypothesis

Metastasis is "the spread of cells from a primary neoplasm to distant sites where they grow" [5] and is the cause of 90% of cancer deaths [6]. Dissemination of cancer cells usually occurs through one of three pathways: 1) direct seeding; 2) lymphatic spread; and 3) haematogenous spread. Metastasis regularly occurs at predictable locations. For example, breast carcinoma commonly metastasises to bone, liver and lung. The predictable nature of metastasis allows the clinician to screen for tumour spread before deciding on suitable therapy.

Over the years, there have been two main hypotheses put forward to explain these clinical observations. Over a century ago, Dr Stephen Paget [7] proposed the "seed and soil" hypothesis, based on autopsy reports of over 700 women who had died from breast cancer. The hypothesis postulated that metastasis is not a random process, but occurs when the tumour cell (the "seed") has a special affinity for certain organs (the "soil").

Forty years later, Ewing [8] proposed an anatomical-mechanical theory, stressing the importance of the circulatory anatomy in determining metastasis. If Ewing's theory is correct, peritoneovenous shunt insertion as a palliative measure in malignant ascites should result in increased metastasis to the lung. This, however, is not the case [9].

Isiah Fidler [10] has provided an updated definition of the "seed and soil" hypothesis, based upon three principles:

i) neoplasms are biologically diverse and contain subsets of cells with varying properties, such as angiogenesis or invasiveness

ii) natural selection occurs within tumours for cells that have metastatic properties

iii) metastasis is dependent on the successful interaction between tumour cells and homeostatic mechanisms.

There are many properties of potential target organs that affect the likelihood of metastasis to that site confirming Paget's "seed and soil" hypothesis:

1) Organ-specific cellular adhesion between the tumour cells and cells in the target organ are critical to the process of metastasis.

2) Target organs may secrete chemoattractants which attract tumour cells towards the organ, increasing the likelihood of metastasis. For example, insulin-like growth factor I (ILGF-I) stimulates melanoma cells to grow, survive and migrate, and this process can be inhibited by antibodies against interleukin 8 [11].

3) Growth may be stimulated not only by autocrine factors (produced by the tumour itself), but also by paracrine factors. Indeed, over-expression of cell receptors on tumour cells may allow them to become highly reactive to relatively "normal" levels of growth factors in the microenvironment.

4) The balance between proteases released by the tumour cells, that degrade the extracellular matrix (ECM), and protease inhibitors secreted by the ECM, that block this process, is crucial. Over-expression of the family of tissue inhibitor of matrix metalloproteinases (TIMP) suppresses tumour growth and metastasis [12,13].

5) Tumour cell migration through degraded ECM is organ-dependent. For example, molecules present in lung ECM preparations induced motility in lung colonising tumour cells, whereas liver ECM preparations did not [14].

6) Specific organ environments affect levels of gene expression. For example, when clones of prostate cancer were implanted both in prostate and subcutis, those cells grown in the prostate, a "fertile" soil, expressed much higher levels of EGF-R, IL8 and type IV collagenase, proteins necessary for metastasis [15]. Interestingly, the same cell in different anatomical sites displays varying properties, including their interaction with hormones and production of cytokines.

7) Animal models have shown that induction of lung tissue injury results in increased retention of cancer cells at that site and increased likelihood of pulmonary metastases [16]. It has been suggested that inflammatory cell and cytokine activity at the tumour site is more likely to encourage metastasis rather than produce an effective antitumour response, and cancer susceptibility may be related to polymorphisms of inflammatory cytokine genes [17].

## Conclusion

Cancer patients die of metastatic disease. The development of metastasis is dependent on the interaction between the tumour cell and its environment. Current treatments have focussed on the "seed" with little attention being paid to the "soil". Perhaps it is time to redress this balance given the wealth of evidence implicating the "soil" in the development of metastatic disease.

## References


1. Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma. Cancer 1950; 3: 74-84.
2. Best BG. Renal carcinoma: a ten year review 1971-1981. Br J Urol 1987; 60: 100-102.
3. Heggarty P, McCusker G, Clements WDB. Bilateral breast metastases from a renal carcinoma. Int J Clin Pract 1998; 52: 443-444.
4. Pursner M, Petchprapa C, Haller JO, Orentlicher RJ. Renal carcinoma: bilateral breast metastases in a child. Pediat Radiol 1997; 27: 242-243.
5. Cotran RS, Kumar V, Collins T (eds; 6th edn): Pathologic basis of disease. WB Saunders Co, 1999, Ch 8, pp 260-327.
6. Sporn MB. The war on cancer. Lancet 1996; 347: 1377-1381.
7. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889; 1: 571-573.
8. Ewing J (ed). A Treatise on Tumours (3rd edn). WB Saunders, Philadelphia, 1928.
9. Tarin D, Price JE, Kettlewell MGW et al. Clinicopathological observations on metastasis in man studied in patients treated with peritoneovenous shunts. Br Med J 1984; 288:749.
10. Fidler IJ. Seed and soil revisited: contribution of the organ microenvironment to cancer metastasis. Surg Oncol Clin N Am 2001; 10: 257-269.
11. Satayamoorthy K, Li G, Vaidya B, Kalabis J, Herlyn M. Insulin-like growth factor-I-induced migration of melanoma is mediated by interleukin-8 induction. Cell Growth Differ 2002; 2:87-93.
12. Jiang Y, Goldberg ID, Shi YE. Complex roles of tissue inhibitors of metalloproteases in cancer. Oncogene 2002; 21: 2245-2252.
13. Brand K. Cancer gene therapy with tissue inhibitors of metalloproteases. Curr Gene Ther 2002; 2: 255-271.
14. Cerra RF, Nathason SD. Organ-specific chemotactic factors present in lung extracellular matrix. J Surg Res 1989; 46: 422-426.
15. Greene G, Kitadai Y, Pettaway CA. Correlation of metastasis-related gene expression with metastatic potential in prostate carcinoma cells implanted in nude mice using an in situ mRNA hybridisation technique. Am J Pathol 1997; 150: 1571.
16. Orr FW, Adamson IYR, Young L. Promotion of pulmonary metastasis in mice by bleomycin-induced endothelial injury. Cancer Res 1986; 2: 891-897.
17. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357: 539-545.