Is lesion location random, and does it really matter?

We physicians are so busy labeling and treating that we don't have the time to question why lesions occur where they do.

Margo S. Clarke, MD

A very peculiar feature of HLA-B27 uveitis is the tendency for one eye to become involved during an attack. This can be so profound that that cells precipitate in the anterior chamber forming a snowbank appearance. Curiously the other eye is completely unaffected, with not a single visible cell floating in the anterior chamber. Clearly the immune system has the ability to discriminate between the two eyes, yet why this occurs is a complete mystery. What is fascinating is that some individuals will repeatedly have an attack in one eye while others will flip-flop between eyes in a seemingly unpredictable fashion. These oddities happen consistently, but in a busy practice these observations simply help to confirm the diagnosis of HLA-B27 iritis. We think it is strange that iritis occurs this way but perhaps these oddities are clues to finding the cause of immune misdirection. More importantly, finding answers may lead to truly definitive treatment rather than symptom control.

Dr Clarke is a clinical assistant professor in the Department of Ophthalmology and Visual Sciences at the University of British Columbia. She is now retired. Dr Clarke's additional areas of special interest include immunology, developmental biology, and genetics.

This article has been peer reviewed.

What I have described for iritis is not unique. Many inflammatory conditions occur asymmetrically and at very select locations. These specific features of preferred sites of pathology are used in determining a differential diagnosis. Why each disease has susceptible anatomic sites is often unknown. Although rheumatoid arthritis involves the metacarpophalangeal joint and not the distal interphalangeal joint, and this pattern of involvement assists diagnostically, we don't question why the distal interphalangeal joint is spared in rheumatoid arthritis yet involved with psoriatic arthritis. Similarly psoriasis tends to involve extensor skin surfaces and each dermatological condition has specified regions of involvement, but there is currently very little data to explain these patterns.

Degenerative diseases also occur in specified sites, and as imaging technology advances it has been noted that there is often directional evolution. Asymmetrical presentation occurs frequently, Parkinson disease being a classic example of unilateral onset. If we perceive asymmetry and lesion site to be random, then we limit the observations that will be made. If we are willing to imagine that tissue that appears to be the same microscopically is in fact molecularly different and that these variances may determine why lesions occur where they do, then asymmetry and directional evolution become powerful clues that can assist our understanding of disease mechanism, which could lead to more specific therapy.

Amazing developmental biology has made great strides in determining the molecular organization that guides assembly of all body sites, and significant portions of this molecular map persist in adult tissue. Remarkably, the blueprint for the body as a whole and for each organ follows a repetitive plan drawn on coordinates (head-tail, back-front, and left-right). Hence each position in the body has molecular coordinates where tissue varies along these axes and the variances can create differential resistance or susceptibility to disease and may explain why all tissue does not succumb simultaneously.

Another fascinating finding in developmental biology is that the mesoderm (fibroblasts and their close relatives in other tissue) carries most of the position code. This was illustrated in chicks that had epithelium from the wing switched to the location where a leg was to develop: scales appeared instead of feathers, hence determining that the mesoderm directed the options inherent in the epithelium. Of relevance to the role of mesoderm in human adult tissue, fibroblasts were cultured from 43 body sites and a position code, analogous to a postal code, was identified unique to each body site, yet following developmental coordinates. Since

Continued on page 500

Continued from page 499

then fibroblasts from many organs have been examined with similar findings. The concept advanced is that positional variances present in fibroblasts then direct changes in skin and hair, explaining the different patterns present over the surface of the body. Understanding the combinatorial regulatory modules that define dermatological patterns remains one of the goals of future research. Perhaps one day the molecular meaning of the lupus butterfly rash will be known.

Spectacular progress has occurred in the field of genetics in the last few decades and it is clear that the further one goes into genetic analysis the more complex it becomes. Each disease is recognized to exhibit heterogeneity. With each person averaging a base-pair substitution every 2000 base pairs, the implication is that with 3 billion base pairs in our genome we each harbor over a million base-pair variances. Although the vast majority of these changes have little impact on the quality or quantity of the proteins we produce, it is easy to understand why there is inter-individual variation in all diseases. Hence any feature of a disease where there is a constant provides an important clue to unraveling disease mechanism. To ignore the cause of asymmetry in HLA-B27 iritis, and not determine the cause for distal interphalangeal involvement in psoriatic arthritis or the reason for distal to proximal spread in dermatomyositis, may mean that valuable clues are being missed. Mechanisms to use these clues include comparative omics by site and phenotyping in genome-wide association studies according to lesion site and directional evolution. In select diseases these approaches are being pursued in part.

Unfortunately as clinicians we are so busy diagnosing and treating diseases that getting the job done and staying on top of recent advances consumes our time and energy. We have been saturated with data to memorize, and asking why has often been shelved. Recently it has been reported that the top-earning treatments for the pharmacological industry are biologicals. And the focus of research is increasingly directed at new biologicals rather than traditional small-molecule drugs. The expense of this approach is concerning. Clearly one can understand that financial incentives direct pharmaceutical research, but as patient advocates we need to foster alternative treatment directions.

This article is written with hope that physicians in clinical practice—especially those new to practice—will become curious, if they are not already, and that through their patient encounters they will continue to question current concepts and form alliances with researchers to pursue questions that address basic concepts.

Lesion location is not random. It is generated by a combination of phenotype variances superimposed on a core developmental map altered by circumstances such as aging, infection, and trauma, and further modified by the visiting immune system that can react appropriately, overreact, or underreact according to clues from the tissue or its innate predecessors. It is all logical but it depends on complex overlapping databases that are inherently faulty if the developmental map is absent. The constant features of location, direction, and asymmetry are potent allies in the quest to ultimately find new specific, definitive treatments. BCMJ

Competing interests

None declared.