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EDITORIAL

Autologous GVHD?

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INTRODUCTION

> `They do certainly give very strange and newfangled names to diseases.'
>
> Plato

Physicians love to name diseases for many reasons such as effectively communicating with colleagues. Lexicologists refer to this practice as creating jargon, namely technical terminology or the characteristic idiom of a special activity or group. It is equally valid to define jargon as an obscure and often pretentious language marked by circumlocutions and long words. When disease names are descriptive, widely and uniformly understood they are useful. There are substantial problems, however, when a jargon term is imprecise, incorrect and/or mis-understood.[1] This situation is especially so when a disease name, label or diagnosis implies an etiology unproved, inaccurate or both.

Autologous GVHD or auto-GVHD is a glaring example of jargon at its worst. Auto-GVHD is widely applied to a complex of clinical, laboratory and sometimes histological features resembling those occurring in persons thought to have acute GVHD after an allotransplant, but in this instance occurring after an autotransplant or a transplant from a genetically identical twin. The label auto-GVHD implies that the clinical, laboratory and histological features observed are mediated by immune-competent cells in the graft directed against disparate histocompatibility Ags of the host or recipient. Such a mechanism is plausible in the setting of an allotransplant, but difficult (though not impossible) to conceptualize when the donor and recipient (host) are genetically identical. Here we take a closer look at whether the label auto-GVHD makes sense.

WHAT IS ACUTE GVHD?

In 1951, Lorenz *et al.*[2] noted a strange syndrome in irradiated rodents given BM and spleen cell transplants from genetically disparate donors. Their discovery was accidental. In most experiments, irradiated and transplanted mice were killed soon after they had hematological recovery (to save costs). In this instance a cage of mice was misplaced in the National Institutes of Health vivarium. When the cage was later recovered, the mice were noted to have weight loss, diarrhea and coat changes. Because early death from BM failure after high-dose radiation was termed primary disease, this syndrome was termed secondary disease. But secondary to what?

The above is an example of labeling diseases we don't understand, but at least in this instance with no etiological implication. In 1955 Main and Prehn[3] reported *secondary disease* in mice when BM or spleen cells from a parent were injected into an unirradiated F1 hybrid, but not in the converse. This experiment proved secondary disease was caused by donor immune cells recognizing and reacting to disparate host histocompatibility Ags. But, alas, the situation proved to be more complex. For example, Jones *et al.*[4] and van Bekkum *et al.*[5] showed parental BM and spleen cells injected into irradiated F1 mice produced GVHD in eubiotic but not in gnotobiotic mice. Also, Brandon *et al.*[6] found antibiotic therapy of mice before syngeneic transplants with cyclosporine prevented development of clinical and pathological features of acute GVHD that occurred when antibiotics were not given. These data imply acute GVHD is a complex process involving genetic disparities with an appropriate vector between donor immune cells and the host, but also other variables such as infection state.

DIAGNOSIS OF ACUTE GVHD BY CLINICAL AND LABORATORY CRITERIA

Unfortunately, the situation in humans is even more complex. Several criteria for diagnosing acute GVHD in humans are based on clinical and laboratory features.[7–10] Each system has advantages and disadvantages, but the important point is these systems differ in their definition of who has acute GVHD. Moreover, there is substantial inter-observer variability in diagnosing acute GVHD using the same classification scheme.[11–14] Finally, the sensitivity and specificity of diagnosing acute GVHD using any of these classifications are unknown.

Recently, Paczesny *et al.*[15] described a biomarker panel associated with the clinical and pathological diagnosis of acute GVHD in allotransplant recipients. Subjects thought to have acute GVHD had increased serum concentrations of IL-2Rα, TNF-R1, hepatocyte growth factor and IL-8. This predictive panel should not be mistaken for a test to determine who has acute GVHD because these factors are inflammatory markers that predict non-relapse mortality, not acute GVHD.

The standard approach to evaluating a diagnostic test is to estimate the sensitivity and specificity, usually derived from a receiver–operator curve or by net reclassification improvement.[16] To do this requires knowing who has and who does not have the condition being studied. With this in mind, consider diagnostic tests of acute GVHD. Because we lack precise knowledge of who has and who does not have acute GVHD, it is impossible to calculate the sensitivity and specificity or the value of net reclassification improvement for any test or combination of tests. The optimal situation for an individual is to derive a best estimate value and confidence or credibility interval (the Bayesian equivalent) of the probability that an individual has acute GVHD. However, even when this best estimate value is high, the confidence or credibility interval may be very large. Thus, we are uncertain whether the individual really has acute GVHD. A better approach is to designate an individual as likely, uncertain or unlikely to have acute GVHD. It follows we are at a loss to accurately determine the sensitivity and sensitivity of diagnostic tests for acute GVHD.

DIAGNOSIS OF ACUTE GVHD BY HISTOLOGIC CRITERIA

Can this issue regarding who has acute GVHD be resolved using histologic criteria? Unfortunately, no. Acute GVHD of the skin is said to be characterized by several distinctive features, but none is specific and similar skin abnormalities occur in many other conditions.[7,11,12] There are similar limitations to diagnosing gastrointestinal and liver acute GVHD.[14,17–18] For example, radiation exposure, drugs and infection produce similar abnormalities in the skin and gut as acute GVHD.[19–23] The time at which

these abnormalities are detected may help distinguish acute GVHD from radiation and drug-induced tissue damage, but this is not always so.[14] Several examples of the difficulty in using histological criteria to diagnose acute GVHD are explained below.

Kohler *et al.*[12] compared the histological features of skin biopsies obtained from persons classified as having ⩾grade-2 GVHD by clinical and laboratory criteria with the biopsies of persons whose initial clinical and laboratory features were consistent with GVHD but whose clinical course did not progress to ⩾grade-2 clinical acute GVHD. Biopsies were reviewed by two pathologists blinded to the clinical and laboratory data. Sixteen histological parameters were considered alone or combined, none of which successfully discriminated between subjects considered to have or not have acute GVHD. When more stringent criteria were applied, 30% of the biopsies were judged as false positives. Over 50% false positives were reported using other (mostly clinical) acute GVHD criteria.

CAN ACUTE GVHD BE ACCURATELY DIAGNOSED BASED ON CLINICAL OR LABORATORY FEATURES?

No. Sale *et al.*[11] studied skin biopsies of recipients of allo-, auto- and genetically-identical twin transplants in persons with leukemia reviewed by three masked pathologists. Changes compatible with ⩾grade-2 acute GVHD were seen in 4 of 6 autotransplant recipients and 6 of 10 genetically identical twin transplant recipients. Importantly, there was substantial discordance between observers in all instances, including allotransplant recipients with complete concordance in only one-third of cases; often a different diagnosis was given by each pathologist. The authors reported rates for false positives and false negatives, but such an exercise does not make sense as we do not know which subjects had acute GVHD.

Hood *et al.*[24] reported rash with skin biopsy changes compatible with grade-2 GVHD in 8% of 115 recipients of auto- and genetically-identical twin transplants between 1977 and 1984. Typically the rash was self-limited. Some subjects received systemic corticosteroids. The cases were reported as having acute skin GVHD. Subsequently, there have been many reports of auto-GVHD.[25–30] Most studies report clinical and laboratory features, and sometimes biopsy findings consistent with acute GVHD usually within the first month post transplant. Typically these abnormalities improved after therapy with corticosteroids, but there are no controlled studies to show these abnormalities might not have resolved without therapy. Also, many disorders resembling acute GVHD may respond to corticosteroids.

In 2004, Adams *et al.*[28] reported histology-based data of acute GVHD in 21 of 119 (18%) recipients of genetically identical twin transplants. Clinical abnormalities were mostly self-limited or improved after corticosteroids and no subject developed chronic GVHD. One subject with AML died from what was described as acute GVHD. Monozygosity of donor and recipient, however, was not convincingly proved by molecular markers. Moreover, we need to acknowledge that genetically identical twins are not always genetically identical.[31]

Bauer *et al.*[32] analyzed skin biopsies from 38 persons receiving autotransplants or intensive chemotherapy but no transplant for diverse cancers. In one-third of cases the reviewers were unable to distinguish the histological features of skin biopsies in those without GVHD from those reported as having grade-2 GVHD. Several similar studies report comparable data.[33] Were one to generate a receiver–operator curve for diagnosis of acute GVHD from skin biopsies, the AUC would not show a high degree of specificity or sensitivity. The sum of these data suggests results of biopsies, especially of skin, are not a reliable basis on which to diagnose acute GVHD.

A striking observation regarding autologous GVHD after autotransplants is the lack of convincing reports of chronic GVHD in this setting. This condition is very unlike the situation after allotransplants where acute and chronic GVHD are highly confounded. This implies either that acute GVHD occurring after an auto- or twin-transplant is biologically distinct from that occurring after an allotransplant, or that auto-GVHD is not really GVHD.

WHAT MIGHT UNDERLIE AUTO-REACTIVITY AFTER AUTO- OR GENETICALLY-IDENTICAL TWIN TRANSPLANTS

Several investigators have proposed that persisting fetal cells in a parous woman who donates BM or blood cells might contribute to or cause acute GVHD in a genetically identical twin recipient. Fetal micro-chimerism in maternal circulation has been observed several decades post partum. One study found male DNA in about one-third of 29 hematopoietic growth factor-mobilized blood mononuclear cell collections in parous female donors.[34] Adams *et al.*[28] found a significant association between donor or recipient parity and acute GVHD as 21 of 119 (18%) syngeneic transplant recipients developed this syndrome. Kline *et al.*[35] also reported increased diagnosis of auto-GVHD in women. The underlying notion is fetal immune cells persisting in a parous female donor could recognize recipient tissues as foreign, whereas persisting fetal cells in a parous female recipient could be a target of donor immune cells.

Another confounder is the pretransplant conditioning regimen. In the twin transplant cohort reviewed above by Adams *et al.*,[28] use of the conditioning regimen containing BU, melphalan and thiotepa was significantly associated with developing acute GVHD features. In a study of 40 persons with aplastic anemia given genetically identical twin transplants, 17 received pre-transplant conditioning while 23 subjects did not. The only four subjects who developed acute GVHD had received pre-transplant conditioning.[36] These data suggest either pre-transplant conditioning is a prerequisite for developing acute GVHD or, more likely, there is confusion in distinguishing the effects of pre-transplant conditioning from acute GVHD.

Based on pre-clinical animal models, post-transplant immunotherapy approaches with agents such as cyclosporine have been developed. Immunotherapy after autologous BM transplant appears to induce a graft-versus-neoplasm effect, the hypothesis being that T-cell subsets are modified and result in an autoimmune state. Several groups extended this approach to the clinical setting. In the most recent, prospective, randomized study, 51 poor-risk lymphoma patients receiving mobilized blood grafts were assigned to receive either cyclosporine with or without IL-2 and γ-IFN ($n=24$), or no post-remission therapy ($n=27$).[23] Only four subjects developed features resembling auto-GVHD. This finding is in marked contrast to the majority of historically treated patients given autologous BM, as opposed to mobilized blood used in this study. Further, the antitumor effect in the treated group did not differ when compared to the 27 patients not given post-transplant therapy.

Without definitive evidence of a graft-mediated immune attack against the host, it is difficult to designate someone as having auto-GVHD. Confounding entities resembling acute GVHD include bacterial, fungal and viral infections, drug reactions, tissue damage from pre-transplant drugs and radiation, and other effects.[7,13,18–22,37–38] There is no reason a transplant recipient cannot have more than one of these confounders. The bottom line is there are no convincing data to show that persons said to have auto-GvHD really have this disease, or that this disease really exists.

A MODEST PROPOSAL ('FOR PREVENTING THE CHILDREN OF POOR PEOPLE IN IRELAND FROM BEING A BURDEN TO THEIR PARENTS OR COUNTRY, AND FOR MAKING THEM BENEFICIAL TO THE PUBLIC.' JONATHAN SWIFT 1729)

As we discussed, the term auto-GVHD is the worst type of jargon. First, it implies that there is such an entity. Second, if auto-GVHD exists, it implies we know who has it. Third, it implies an etiological basis in a specific case, which is unproved. Lastly, this designation in most persons is almost certainly incorrect. The complete absence of chronic GVHD after autotransplants suggests the designation of auto-GVHD is often wrong. We make this statement because chronic GVHD is a distinct entity highly correlated with acute GVHD and with few confounders. Others may argue acute and chronic GVHD have different biological bases and therefore there need not be concordance. Because of all these considerations, we suggest abandoning the term auto-GVHD until, if ever, we have a better understanding whether this condition exists and who has it. Taking an example from Prince (the musician, not Charles), how about renaming it 'the disease formerly known as auto-GvHD'?

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REFERENCES

1 Gale RP, Lazarus HM. 'A rose by any other name would smell as sweet', or would it? *Bone Marrow Transplant* 2013; **48**: 881–883.
2 Lorenz E, Uphoff D, Reid TR, Shelton E. Modification of irradiation injury in mice and guinea pigs by bone marrow injection. *J Natl Cancer Inst* 1951; **12**: 197–201.
3 Main JM, Prehn RT. Successful skin homografts after the administration of high dosage X irradiation and homologous bone marrow. *J Natl Cancer Inst* 1955; **15**: 1023–1030.
4 Jones JM, Wilson R, Bealmear PM. Mortality and gross pathology of secondary disease in germfree mouse radiation chimeras. *Radiat Res* 1971; **45**: 577–580.
5 van Bekkum DW, Roodenburg J, Heidt PJ, van der Waaij D. Mitigation of secondary disease of allogeneic mouse radiation chimeras by modification of the intestinal microflora. *J Natl Cancer Inst* 1974; **52**: 401–406.
6 Brandon JA, Jennings CD, Kaplan AM, Bryson JS. Murine syngeneic graft-versus-host disease is responsive to broad-spectrum antibiotic therapy. *J Immunol* 2011; **186**: 3726–3734.
7 Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009; **373**: 1550–1561.
8 Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J *et al.* 1994 Consensus Conference on acute GVHD grading. *Bone Marrow Transplant* 1995; **15**: 825–828.
9 Deeg HJ, Antin JH. The clinical spectrum of acute graft-versus-host disease. *Semin Hematol* 2006; **43**: 24–31.
10 Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ *et al.* National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005; **11**: 945–956.
11 Sale GE, Lerner KG, Barker EA, Shulman HM, Thomas ED. The skin biopsy in the diagnosis of acute graft-versus-host disease in man. *Am J Pathol* 1977; **89**: 621–636.
12 Kohler S, Hendrickson MR, Chao NJ, Smoller BR. Value of skin biopsies in assessing prognosis and progression of acute graft-versus-host disease. *Am J Surg Pathol* 1997; **21**: 988–996.
13 Horn TD, Redd JV, Karp JE, Beschorner WE, Burke PJ, Hood AF. Cutaneous eruptions of lymphocyte recovery. *Arch Dermatol* 1989; **125**: 1512–1517.
14 Sale GE, Shulman HM, McDonald GB, Thomas ED. Gastrointestinal graft-versus-host disease in man. A clinicopathologic study of the rectal biopsy. *Am J Surg Pathol* 1979; **3**: 291–299.
15 Paczseny S, Krijanovski OI, Braun TM, Choi SW, Clouthier SG, Kuick R *et al.* A biomarker panel for acute graft-versus-host disease. *Blood* 2009; **113**: 273–278.
16 Pencina MJ, D'Agostino RB, Pencina KM, Janssens CJW, Grrenland P. Interpreting incremental value of markers added to risk prediction models. *Am J Epidemiol* 2012; **176**: 473–481.
17 Lerner KG, Kao GF, Storb R, Buckner CD, Clift RA, Thomas ED. Histopathology of graft-vs-host reaction (GvHR) in human recipients of marrow from HL-A-matched sibling donors. *Transplant Proc* 1974; **6**: 367–371.
18 Holmberg L, Kikuchi K, Gooley TA, Adams KM, Hockenbery DM, Flowers ME *et al.* Gastrointestinal graft-versus-host disease in recipients of autologous hematopoietic stem cells: incidence, risk factors, and outcome. *Biol Blood Marrow Transplant* 2006; **12**: 226–234.
19 LeBoit PE. Subacute radiation dermatitis: a histologic imitator of acute cutaneous graft-versus-host disease. *J Am Acad Dermatol* 1989; **20**: 236–241.
20 Horn TD. Acute cutaneous eruptions after marrow ablation: roses by other names? *J Cutan Pathol* 1994; **21**: 385–392.
21 Fitzpatrick JE. The cutaneous histopathology of chemotherapeutic reactions. *J Cutan Pathol* 1993; **20**: 1–14.
22 Yokel BK, Friedman KJ, Farmer ER, Hood AF. Cutaneous pathology following etoposide therapy. *J Cutan Pathol* 1987; **14**: 326–330.
23 Bolanos-Meade J, Garett-Mayer E, Luznik L, Anders V, Webb J, Fuchs EJ *et al.* Induction of autologous graft-versus-host disease: results of a randomized prospective clinical trial in patients with poor risk lymphoma. *Biol Blood Marrow Transplant* 2007; **13**: 1185–1191.
24 Hood AF, Vogelsang GB, Black LP, Farmer ER, Santos GW. Acute graft-vs-host disease: development following autologous and syngeneic bone marrow transplantation. *Arch Dermatol* 1987; **123**: 745–750.
25 Rappeport J, Mihm M, Reinherz E, Lopansri S, Parkman R. Acute graft-versus-host disease in recipients of bone-marrow transplants from identical twin donors. *Lancet* 1979; **2**: 717–720.
26 Drobyski WR, Hari P, Keever-Taylor C, Komorowski R, Grossman W. Severe autologous GVHD after hematopoietic progenitor cell transplantation for multiple myeloma. *Bone Marrow Transplant* 2009; **43**: 169–177.
27 Lazarus HM, Sommers SR, Arfons LM, Fu P, Ataergin SA, Kaye NM *et al.* Spontaneous autologous graft-versus-host disease in plasma cell myeloma autograft recipients: flow cytometric analysis of hematopoietic progenitor cell grafts. *Biol Blood Marrow Transplant* 2011; **17**: 970–978.
28 Adams KM, Holmberg LA, Leisenring W, Fefer A, Guthrie KA, Tylee TS *et al.* Risk factors for syngeneic graft-versus-host disease after adult hematopoietic cell transplantation. *Blood* 2004; **104**: 1894–1897.
29 Cogbill CH, Drobyski WR, Komorowski RA. Gastrointestinal pathology of autologous graft-versus-host disease following hematopoietic stem cell transplantation: a clinicopathological study of 17 cases. *Mod Pathol* 2011; **24**: 117–125.
30 Gluckman E, Devergie A, Sohier J, Saurat JH. Graft-versus-host disease in recipients of syngeneic bone marrow. *Lancet* 1980; **1**: 253–254.
31 Bruder CE, Piotrowski A, Gijsbers AA, Andersson R, Erickson S, Diaz de Stahl T *et al.* Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. *Am J Hum Genet* 2008; **82**: 763–771.
32 Bauer DJ, Hood AF, Horn TD. Histologic comparison of autologous graft-vs-host reaction and cutaneous eruption of lymphocyte recovery. *Arch Dermatol* 1993; **129**: 855–858.
33 Li N, Guthrie KA, Storer BE, Martin PJ, Sale GE, Argenyi ZB *et al.* Keratinocyte dysplasia in hematopoietic stem cell transplantation recipients in the day-28-to-84 posttransplantation period. *Biol Blood Marrow Transplant* 2012; **18**: 1281–1286.
34 Adams KM, Lambert NC, Heimfeld S, Tylee TS, Pang JM, Erickson TD *et al.* Male DNA in female donor apheresis and CD 34-enriched products. *Blood* 2003; **102**: 3845–3847.
35 Kline J, Subbiah S, Lazarus HM, van Besien K. Autologous graft-versus-host disease: harnessing anti-tumor immunity through impaired self-tolerance. *Bone Marrow Transplant* 2008; **41**: 505–513.
36 Hinterberger W, Rowlings PA, Hinterberger-Fischer M, Gibson J, Jacobsen N, Klein JP *et al.* Results of transplanting bone marrow from genetically identical twins into patients with aplastic anemia. *Ann Intern Med* 1997; **126**: 116–122.
37 Castaño E, Rodríguez-Peralto JL, López-Ríos F, Gómez C, Zimmermann M, Iglesias Díez L. Keratinocyte dysplasia: an usual finding after transplantation or chemotherapy. *J Cutan Pathol* 2002; **29**: 579–584.
38 Burgdorf WH, Gilmore WA, Ganick RG. Peculiar acral erythema secondary to high-dose chemotherapy for acute myelogenous leukemia. *Ann Intern Med* 1982; **97**: 61–62.